

No. 23-2017

**UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT**

DNA GENOTEK INC.,

Plaintiff-Appellant,

v.

SPECTRUM SOLUTIONS LLC,

Defendant-Appellee.

Appeal from the United States District Court for the Southern District of
California, No. 3:21-cv-00516-RSH-DDL, Judge Robert S. Huie

**DNA GENOTEK INC.'S
OPENING BRIEF**

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SEPTEMBER 28, 2023

U.S. Patent No. 10,619,187 Claim 1

1. A device for receiving and preserving nucleic acid in a biological sample, said device comprising:

- a. one or more walls defining a containment vessel having a top having an opening, and a closed bottom having a sample receiving area for holding said biological sample, said opening for receiving a liquid sample and for sealably receiving a sealing cap, said top having an opening for receiving a biological sample from the mouth of a user and further comprising at least one marking on said one or more walls which corresponds to a fluid volume in the sample receiving area;
- b. a reagent compartment having a barrier, said barrier sealing and containing reagents in said reagent compartment and capable of disestablishment to release said reagents into the sample receiving area;
- c. reagents in the reagent compartment for preserving nucleic acids potentially present in the sample wherein said reagents comprise a denaturing agent, a chelator and a buffer agent; and,
- d. the sealing cap, whereby the device is configured such that, when sealably closing said opening with said sealing cap, the barrier mechanically disestablishes to release said reagents to form a mixture of reagents and said biological sample wherein said buffering agent maintains a pH of said mixture equal to or above 5.0 to preserve nucleic acids potentially present in the sample.

U.S. Patent No. 11,002,646 Claim 1

1. A kit for collecting and preserving a biological sample, the kit comprising:

- a sample collection vessel, the sample collection vessel comprising: a sample collection reservoir having an opening configured to receive the biological sample from a user into the sample collection reservoir; a connection member disposed on an exterior portion of the sample collection vessel and adjacent to the opening;
 - a cap, the cap comprising: a reagent chamber configured to store a reagent; and a complementary connection member configured to engage the connection member of the sample collection vessel; and
 - a movable annular valve configured to associate with the cap and with the opening of the sample collection reservoir, the movable annular valve comprising: an inner cylinder in fluid-tight association with the cap and comprising a sidewall, the sidewall comprising a fluid vent; and an outer cylinder in fluid-tight association with the inner cylinder and associated with the opening of the sample collection reservoir, the outer cylinder comprising an aperture defined by an interior sidewall of the outer cylinder,
- wherein the aperture accommodates at least a portion of the inner cylinder,
- wherein the interior sidewall obstructs the fluid vent when the movable annular valve is closed,
- and
- wherein the interior sidewall does not obstruct the fluid vent when the movable annular valve is open.

CERTIFICATE OF INTEREST

Counsel for DNA Genotek Inc. certify under Federal Circuit Rule 47.4 that the following information is accurate and complete to the best of their knowledge:

1. **Represented Entities.** Provide the full names of all entities represented by undersigned counsel in this case.

DNA Genotek Inc.

2. **Real Parties in Interest.** Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.

None.

3. **Parent Corporations and Stockholders.** Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.

DNA Genotek Inc. is a wholly owned subsidiary of OraSure Technologies, Inc. Blackrock Inc. owns 10% or more of OraSure Technologies, Inc.'s stock.

4. **Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court.

MORRISON & FOERSTER LLP: David D. Cross; Candice F. Heinze (no longer with firm); and John R. Lanham.

5. **Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

Yes, see separately filed notice.

6. **Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees).

Not applicable.

Dated: September 28, 2023

/s/ Brian R. Matsui

Brian R. Matsui

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STATEMENT OF RELATED CASES

No appeal from this proceeding on U.S. Patent Nos. 10,619,187 (the '187 patent) and 11,002,646 (the '646 patent) owned by DNA Genotek Inc. (Genotek) has previously been before this Court or any other court. The '646 patent is the subject of IPR2022-01347, which is pending before the Patent Trial and Appeal Board. Counsel for Genotek know of no other cases pending in this Court or any other court that will directly affect or be affected by this Court's decision in this appeal.

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). It entered final judgment on June 7, 2023. Genotek filed a timely notice of appeal from that judgment on June 8, 2023. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

INTRODUCTION

Genotek is widely recognized as a leading innovator in the field of biological sample collection devices. This appeal involves two of Genotek’s patents, both apparatus claims directed to biological sample collection kits. In construing those claims, the district court committed a fundamental claim construction error: it limited the claims to specific embodiments disclosed in the specifications. It justified that reading because it interpreted language from the specifications as either disclaiming or redefining the claim terms’ ordinary and customary meaning. Yet as this Court has repeatedly explained, the standard for lexicography or disclaimer is exacting, and requires unmistakable evidence that the patentee intended to depart from a term’s ordinary and customary meaning. The specifications here come nowhere close to satisfying that standard. Instead, the district court narrowed the claims to the precise teachings of preferred embodiments and relied on irrelevant extrinsic evidence—all of which this Court has warned against.

For the ’187 patent, the district court rewrote Genotek’s claims. The ’187 patent recites a device for collecting and preserving a biological sample. The claims require a structure—a “reagent compartment”—with specific structural features. Yet the district court created an additional requirement: a specific location in the device where the reagent compartment must be found. The reason why: it concluded that Genotek had disclaimed other locations simply because certain

embodiments purported to show the reagent compartment in one location. And it did so in the absence of any evidence that this location was “essential” to the invention. But time and again, this Court has rejected that approach to construing claims: just because the specification might describe an invention one way does not mean that the claims are limited only to that way.

The ’646 patent also claims a biological sample collection kit. As is common, those apparatus claims include a preamble identifying one beneficial use of the apparatus—“for collecting and preserving a biological sample.” The district court redrafted that preamble as a functional requirement that the apparatus must prevent “cells in the biological sample from having their antigens degraded such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome.” But this Court has repeatedly refused to read preambles that merely provide an intended use for a claimed apparatus as limiting. Indeed, it has cautioned against creating functional requirements for apparatus claims, particularly when the body of the claim provides all the necessary structures. And regardless, nothing in the law or facts supports the district court’s wholesale importation of passages from the specification to create a highly technical 30-word construction of the simple term “preserving a biological sample.”

The district court’s claim constructions should be reversed and the judgment of non-infringement should be vacated.

STATEMENT OF THE ISSUES

1. Whether to vacate the judgment of noninfringement on the '187 patent because the district court erred in construing “reagent compartment” as “region or section of the containment vessel.”

2. Whether to vacate the judgment of noninfringement on the '646 patent because the district court erred in construing “preserving a biological sample” as “preventing cells in the biological sample from having their antigens degraded such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome.”

STATEMENT OF THE CASE

A. Genotek’s Asserted Patents And Spectrum’s Infringing Products

Genotek is a leading innovator in the field of biological sample collection. It has revolutionized the nucleic acid (DNA and RNA) collection market with products that provide substantial advantages over traditional methods of biological sample collection. During the COVID-19 pandemic, Genotek became a leader in providing reliable saliva collection devices for COVID-19 testing. *Time* magazine named Genotek’s OMNIgene Oral saliva collection kit for COVID-19 samples one of the Best Inventions of 2020.¹ This appeal involves two of Genotek’s patents.

¹ See *The Best Inventions of 2020: At-Home Sampling: OraSure OMNIgene Oral*, Time Mag. (Nov. 19, 2020), <https://time.com/collection/best-inventions-2020/5911390/orasure-omnigene-oral>.

1. The '187 patent

The '187 patent claims a device for collecting and preserving biological samples, such as DNA present in saliva.

DNA can be extracted from almost every type of cell in the human body. Appx131 (col.1:27-28). Saliva, however, is a particularly “reliable source of genomic DNA” and a promising “rival to venous blood samples.” Appx131 (col.2:10-16). That is because compared to saliva collection, blood collection is more painful and invasive, poses additional risks, and requires additional training. Appx131 (col.1:38-55). Other ways to collect biological samples for DNA, such as cheek swabs, recover a very small number of cells and thus, a very small amount of DNA. Appx131 (col.1:56-67). As a result, the inventors recognized “a need for a product that would allow saliva to become a standard reliable source of DNA from an individual” (Appx131 (col.2:35-39))—particularly as the “use of DNA-based analysis in forensics, law enforcement, military, human medicine, veterinary medicine, and research” has increased (Appx131 (col.2:35-39)). The apparatus claimed by the '187 patent fulfills that need: “a novel collection device useful for collecting a biological sample from a subject” and for mixing that sample “with a composition intended to stabilize, preserve, or facilitate the recovery of components of the sample.” Appx137 (col.14:40-44).

Claim 1 is the only independent claim, and it states:

1. A device for receiving and preserving nucleic acid in a biological sample, said device comprising:
 - a. one or more walls defining a containment vessel having a top having an opening, and a closed bottom having a sample receiving area for holding said biological sample, said opening for receiving a liquid sample and for sealably receiving a sealing cap, said top having an opening for receiving a biological sample from the mouth of a user and further comprising at least one marking on said one or more walls which corresponds to a fluid volume in the sample receiving area;
 - b. a *reagent compartment* having a barrier, said barrier sealing and containing reagents in said reagent compartment and capable of disestablishment to release said reagents into the sample receiving area;
 - c. reagents in the *reagent compartment* for preserving nucleic acids potentially present in the sample wherein said reagents comprise a denaturing agent, a chelator and a buffer agent; and,
 - d. the sealing cap, whereby the device is configured such that, when sealably closing said opening with said sealing cap, the barrier mechanically disestablishes to release said reagents to form a mixture of reagents and said biological sample wherein said buffering agent maintains a pH of said mixture equal to or above 5.0 to preserve nucleic acids potentially present in the sample.

Appx140 (col.19:34-59) (emphases added). The device of claim 1 thus includes four elements: a containment vessel, a reagent compartment, a sealing cap, and reagents. Each of these elements has specific requirements. The containment vessel, for example, must have specific structures: walls, an opening, and a closed bottom.

Appx140 (col.19:36-37). The reagent must be found in a specific location: “in the reagent compartment.” Appx140 (col.19:49). The sealing cap must be configured to release the reagents. Appx140 (col.19:53-56). And the reagent compartment—the term at issue on appeal—requires a barrier that can be disestablished so that reagents may be released into the sample receiving area in the containment vessel. Appx140 (col.19:45-48). The claim is silent on where the reagent compartment must be located.

Although the specification provides some definitions (Appx134 (col.7:1-62)), “reagent compartment” is not defined. The specification also describes some embodiments of a collection device, but none uses the terms “reagent compartment” or “containment vessel.” These embodiments include “a device for preserving and/or isolating a nucleic acid obtained from a biological sample.” Appx133 (col.6:26-28). In some embodiments, this device includes “a container that has a first region for collecting a biological sample and a second region containing a composition for preserving a nucleic acid, a barrier between the first region [and] the second region that keeps the biological sample and the composition separate.” Appx133 (col.6:28-33).

In another embodiment, the claimed invention discloses the compartment for containing the composition for preserving a nucleic acid in the cap of the container: this compartment “contain[s] the agent or agents, such that agents can be kept

separate if desired from each other or from the sample until a predetermined or desired time.” Appx3184. And “[i]n one embodiment th[is] compartment is the underside of the cap of the container.” Appx3184. This embodiment is disclosed in U.S. Provisional Patent Application Ser. No. 60/386,398 (“the ’398 provisional”), which the ’187 patent states is “incorporated herein by reference in its entirety.” Appx131 (col.1:15-20). Figure 2 of the ’398 provisional depicts the “reagent compartment” (3) in the cap:

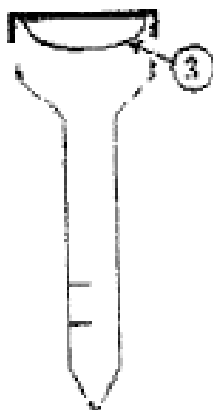


FIGURE 2

Appx3190.

In the ’398 provisional, the reagent compartment in the cap is described as a “small bag” (3). Appx3186. By contrast, when the ’398 provisional describes a reagent compartment in the tube, it refers to a “septum” (4) in Figure 3:



FIGURE 3

Appx3186; Appx3190.

The '187 patent's specification refers to the "bag compartment" that the '398 provisional had described as being in the cap, and it explains that the reagents may be held by that "bag compartment," by a "septum," or by some other specified barrier. Appx138 (col.15:17-20). The patent emphasizes that the "precise way [the nucleic acid-preserving composition] will be introduced will depend upon the container design." Appx138 (col.16:9-12); Appx133 (col.15:17-49).

The patent states that the claims are not limited to the embodiments disclosed in the specification; rather, "the detailed description and the specific examples, while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the

invention will become apparent to those skilled in the art from this detailed description.” Appx134 (col.7:64-8:3).

2. *The '646 patent*

The '646 patent claims a device relating to the collection of biological samples. The patent recognizes a “need for safer and easier to use sample collection devices.” Appx174 (col.4:35-36). To that end, the invention can “provide several advantages over currently available sample collection devices”: for example, the inventive device might use a smaller number of parts, might not require removal or exchange of parts, and might require only minimal manipulation by the donor of the biological sample. Appx174-175 (col.4:62-5:4).

Although the specification also discloses methods and solutions, the '646 patent recites only apparatus claims. Claim 1 is the only independent claim, and it states:

1. A kit for collecting and *preserving a biological sample*, the kit comprising:

a sample collection vessel, the sample collection vessel comprising:

a sample collection reservoir having an opening configured to receive the biological sample from a user into the sample collection reservoir;

a connection member disposed on an exterior portion of the sample collection vessel and adjacent to the opening;

a cap, the cap comprising:

a reagent chamber configured to store a reagent; and

a complementary connection member configured to engage the connection member of the sample collection vessel; and

a movable annular valve configured to associate with the cap and with the opening of the sample collection reservoir, the movable annular valve comprising:

an inner cylinder in fluid-tight association with the cap and comprising a sidewall, the sidewall comprising a fluid vent; and

an outer cylinder in fluid-tight association with the inner cylinder and associated with the opening of the sample collection reservoir, the outer cylinder comprising an aperture defined by an interior sidewall of the outer cylinder,

wherein the aperture accommodates at least a portion of the inner cylinder,

wherein the interior sidewall obstructs the fluid vent when the movable annular valve is closed, and

wherein the interior sidewall does not obstruct the fluid vent when the movable annular valve is open.

Appx183 (col.22:16-47) (emphases added).

At issue on appeal is the phrase “preserving a biological sample,” which appears only in the preamble and states a purpose and intended use for the claimed apparatus. The body of the claim recites structures for the claimed apparatus. These structures include “a sample collection vessel,” “a cap,” and “a movable annular

valve.” Appx183 (col.22:18-47). Each of these structures itself has specific requirements, including, among others, a reservoir, a reagent chamber, and a “connection member” configured to engage different structures. Appx183 (col.22:18-47). The body of the claim lacks any limitation on whether, how, or to what degree the “biological sample” must be preserved.

Like the body of the claim, the specification never uses the term “preserving a biological sample.” It discloses “sample collection *devices*,” “as well as *solutions and methods* for preserving cells of samples collected, and additionally, *methods* for isolating specific cells either collected and/or preserved.” Appx174 (col.4:53-58) (emphases added). When discussing sample collection *device* embodiments, the specification discloses structures, such as “two main mating bodies, a cap and a tube” (Appx175 (col.5:11-12)) and “a cap having an outer wall having an engagement member, and an interior chamber for holding a fluid” (Appx175 (col.5:23-24)). Elsewhere, when describing *solutions* and *methods*, the specification discusses how bodily fluids and cells might be preserved.² For instance, in “some embodiments,” a “solution” is disclosed that “prevent[s] the cells from having their antigens degraded, such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome.” Appx180 (col.16:9-27). Other

² Another patent stemming from a continuation application is directed to those embodiments disclosing the preservation of cells. See U.S. Patent No. 11,549,870.

“[e]mbodiments” contemplate “isolating specific cells either collected and/or preserved.” Appx174 (col.4:53-58) (emphasis added). And the specification teaches that some “embodiments . . . refer to naturally expressed bodily fluids including, for example, saliva and urine”—but that other “embodiments can be used for collection of” other bodily fluids, such as “blood.” Appx175 (col.6:54-60).³

B. District Court Proceedings

Spectrum was formed as a provider of packaging materials, such as glass bottles and cardboard goods. Spectrum entered the sample collection kit market when it began packaging services for Ancestry.com DNA—one of Genotek’s customers. Genotek sued Spectrum for infringing both the ’187 patent and the ’646 patent after Spectrum began making and selling devices to test for RNA. Appx296-297. The accused products are depicted below:

³ It was undisputed that not all biological samples contain cells. As Genotek’s expert explained, and Spectrum did not dispute, “[a] biological sample can contain cells, but a biological sample can also not contain cells.” Appx2559 (Metzker). Urine, for example, may or may not contain cells. Appx2562.



The Spectrum products contain a reagent compartment in the cap of the device. Appx3513; Appx3517; Appx3636-3637.

1. The district court's claim construction ruling

'187 patent. The district court construed claim 1's term "reagent compartment" as a "region or section of the containment vessel." The court did not disagree that the claims' plain text lacks any limitation "requir[ing] that the reagent compartment be located" in any specific part of the device. Appx32. It thought the lack of such an express limitation meant the claim language "is ambiguous as to

where precisely the reagent compartment is located within the claimed device.” Appx33. And it concluded that the specification resolved this purported ambiguity with “several clear disclaimers explaining that the invention claimed in the ’187 Patent features a device with the reagent compartment in the container (*i.e.*, the containment vessel).” Appx44.

According to the district court, these “clear disclaimers” were embodiments disclosing a “container” with a region for collecting a biological sample and a region to contain a reagent. Appx33. Believing that these embodiments “describ[e] the invention as a whole,” the district court concluded that they “constitute[d] a clear disclaimer” of the reagent compartment being placed anywhere else. Appx33; Appx35.

The district court acknowledged that another embodiment (from the ’398 provisional that was incorporated by reference) disclosed a reagent compartment in the cap. Appx36-38. It reasoned, however, that the other embodiments disclosing a container with a reagent compartment “disavow[ed]” what the provisional application disclosed. Appx38. And it concluded that the omission of the provisional application’s embodiment from the ’187 patent’s specification (other than by incorporation) further supported disclaimer. Appx38-40.

Finally, the district court cited a statement Genotek had made during an IPR of an unrelated patent where Genotek described the preferred embodiment of an

international Patent Cooperation Treaty application called Birnboim—the United States counterpart of which is an ancestor of the application that became the ’187 patent. Appx40-41; Appx1518-1566. In the IPR, Genotek described the Birnboim embodiment as disclosing “a rotated screw cap with a ram in the cap and a reagent below a plastic cover in a container.” Appx40-41. The court concluded that Genotek’s statement of “a reagent . . . in the container” described the claimed invention of the ’187 patent “as a whole.” Appx41. The court determined the statement was “highly relevant” evidence supporting its construction. Appx44.⁴

’646 patent. The court concluded that claim 1’s preamble was limiting and then construed the preamble term “preserving a biological sample” to mean “preventing cells in the biological sample from having their antigens degraded such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome.” Appx59.

The district court determined the preamble limited the claims because the phrase “a biological sample” provides antecedent basis for the phrase “the biological sample” in the body of claim 1. Appx61. It then concluded that the phrase “preserving a biological sample” required “preserving cells.” Appx62-63. It did so,

⁴ The district court had construed the term “containment vessel” to mean “container” (Appx21) and then appeared to equate “container” with “containment vessel” whenever it was used in the specification, regardless of context.

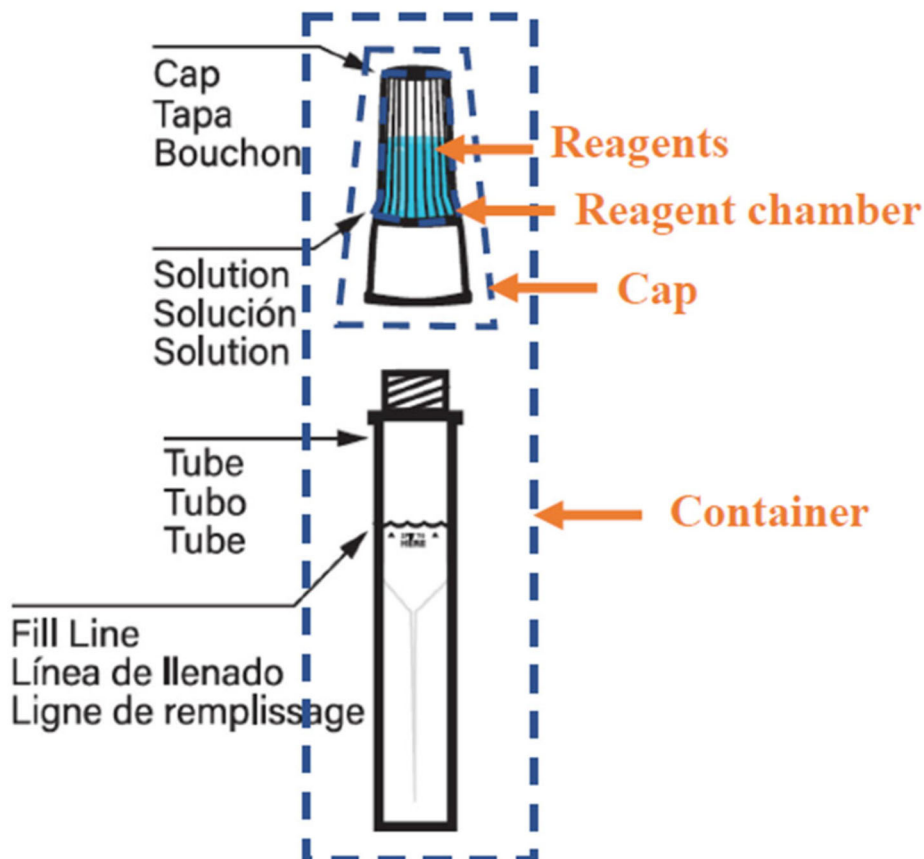
in part, because it had previously construed the term “biological sample” to mean “biological sample containing cells.” Appx57. And the district court cited statements in the specification explaining that the disclosure “relates generally to,” among several other things, “the isolation and preservation of cells.” Appx62-63. The court then reasoned, based on embodiments of solutions and methods for preserving cells (Appx180 (col.16:23-29)), that the specification teaches that “preserving cells” means two things: (1) “preventing the cells from having their antigens degraded,” and (2) “preventing alterations in the cellular epigenome.” Appx64-65.

2. The district court grants summary judgment of noninfringement

Because the district court’s claim constructions foreclosed Genotek’s original infringement contentions, Genotek served amended infringement contentions and conducted extensive testing of Spectrum’s products according to the district court’s construction. Genotek maintained its disagreement with how the district court had construed “reagent compartment” in the ’187 patent and “preserving a biological sample” in the ’646 patent. Appx3635, Appx3691. Even under those constructions, however, Genotek believed Spectrum’s products infringed. Spectrum moved for summary judgment under the district court’s constructions.

For the ’187 patent, Genotek’s expert, Dr. Steven Wereley, explained that Spectrum’s products infringe because they contain a reagent compartment in the

sealing cap, which is part of the “container” or “containment vessel.” Appx3640; Appx84. The following diagram illustrates this theory:



Appx3836.

The district court disagreed. It concluded that Genotek never argued at claim construction that the sealing cap could be part of the containment vessel and, in any event, that the cap and containment vessel had to be distinct structures. Appx87-90. The court further explained that “[i]f the cap is part of the containment vessel, then the containment vessel does not have a top with an opening because the uppermost part or point of the containment vessel would be the top of the cap, which is enclosed and does not have an opening for receiving a cap.” Appx88-89.

The district court also rejected Genotek’s request that the construction of “reagent compartment” be revisited. In doing so, it stated that “its entry of summary judgment of non-infringement” for Genotek’s amended infringement contentions “[was] not based on the ‘reagent compartment’ limitation.” Appx101. Rather, the district court explained that what Genotek called a “container”—which included the cap under the amended infringement contentions—could not be a “containment vessel,” which must have “a top having an opening” that can receive a sealing cap. Appx101. The district court noted that Spectrum had conceded under the original infringement contentions that its products had a “containment vessel,” but the district court concluded that Genotek had “declined to accept that concession” by contending that a containment vessel could include a sealing cap. Appx92 n.7.

For the ’646 patent, the district court first concluded that Genotek had failed to show that Spectrum’s products met one part of the court’s preamble construction—preserving cells by preventing their antigens from being degraded. The court deemed evidence that Spectrum’s products preserved TLR2 antigens insufficient, because it reasoned that preventing cells “from having their antigens degraded” required preservation of every kind of antigen in a biological sample. Appx107. It thus rejected Genotek’s argument that preserving antigens of one type was enough.

Second, the district court concluded that Genotek had failed to produce sufficient evidence that Spectrum's products met another part of the court's preamble construction—preserving cells by preventing changes to the cellular epigenome. The district court's summary-judgment decision expanded on what it means to prevent alteration of the cellular epigenome by pulling the following statement from the specification: "Examples of such alteration include methylation at the 5 position of cytosine in a CpG dinucleotide, acetylation of lysine residues of histones, and other heritable or non-heritable changes that do not result from changes in the underlying DNA sequence." Appx111; Appx180 (col.16:29-31). Based on these "examples," the district court determined that proving that a solution prevented alteration to the cellular epigenome required proving "at the very least" *both* (1) that the solution prevented methylation of cytosine and (2) that the solution prevented acetylation of lysine residues of histones. Appx112-113. Because Genotek's expert had examined only whether methylation had occurred, Genotek's evidence was not enough. Appx110-111.

SUMMARY OF ARGUMENT

I. In construing the term "reagent compartment," the court committed basic claim construction errors.

A. Neither the claim text nor the specification redefines or disclaims the full scope of the "reagent compartment," which by its plain terms can be located

anywhere in the claimed device. The claim text suggests no limit on where the reagent compartment must be located. The specification is similarly devoid of any limiting statements; instead, it simply provides embodiments that describe various options for how the device may be structured. And a provisional application expressly incorporated into the '187 patent in its entirety discloses a reagent compartment in the cap.

B. None of the district court's justifications for construing the reagent compartment as part of the containment vessel withstand scrutiny. First, the court read specification statements that described "aspects" and "desirable" features as disclaimers. But these statements fall far short of this Court's exacting standards for lexicography or disclaimer. In concluding otherwise, the district court gave dispositive effect to the use of the phrase "the invention features" when describing these embodiments. Yet this Court has repeatedly instructed that such language cannot support disclaimer when, as here, there is no indication that a feature is essential to the invention.

The district court also concluded that the omission of an embodiment from the '398 provisional evidenced that embodiment had been disclaimed. In doing so, it cast aside the incorporation-by-reference doctrine for provisional applications, and created a near-categorical rule that anything from a provisional that is omitted in the issued patent is disclaimed.

Finally, the district court was doubly wrong to rely on a statement Genotek had made in an IPR of an unrelated patent. Statements in proceedings on an unrelated patent cannot be a basis for disclaimer. And regardless, that IPR statement was describing an embodiment, not the invention as a whole.

II.A. For the term “preserving a biological sample,” the district court made a threshold error: the term requires no construction. The term appears only in the apparatus claim’s preamble. And where, as here, the preamble merely describes an intended purpose of the apparatus and the body of the claim describes a structurally complete invention, the preamble is not limiting. This is particularly true for the preamble term “preserving,” which is mentioned nowhere in the claim body.

The district court’s sole basis for construing the entire preamble as limiting was that “a biological sample” provides antecedent basis for the claim-body term “the biological sample.” But antecedent basis is relevant only to the extent it signals that the inventor was relying on the preamble to define a claim element. No such reliance exists here. In any event, no justification exists for deeming “preserving”—which provides antecedent basis for nothing in the claims—as limiting. After all, this Court has explained that just because one part of the preamble is limiting does not suggest the entire preamble must be so.

B. Even if the entire preamble limits the claims, no intrinsic or extrinsic evidence supports the court’s highly technical construction of that term. The claim

text and specification point in one direction: preserving a biological sample means slowing degradation of any biological material. The district court wrongly equated “preserving a biological sample” with “preserving cells,” and then imported into the claims the patent’s explanation of that different term—which is used to describe embodiments of unclaimed *methods* and *solutions*, not kits like those claimed by the ’646 patent.

STANDARD OF REVIEW

Claim construction is a question of law that this Court reviews de novo when, as here, the construction is based only on intrinsic and undisputed extrinsic evidence. *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1345 (Fed. Cir. 2020). This Court “review[s] summary judgment rulings under the law of the regional circuit, here the Ninth Circuit.” *Adasa Inc. v. Avery Dennison Corp.*, 55 F.4th 900, 907 (Fed. Cir. 2022). “The Ninth Circuit ‘review[s] the district court’s grant of summary judgment de novo, determining whether, viewing all evidence in the light most favorable to the nonmoving party, there are any genuine issues of material fact and whether the district court correctly applied the relevant substantive law.’” *Id.* (quoting *Kraus v. Presidio Tr. Facilities Div./Residential Mgmt. Branch*, 572 F.3d 1039, 1043-44 (9th Cir. 2009)).

ARGUMENT

I. FOR THE '187 PATENT, THE DISTRICT COURT ERRED IN CONSTRUING THE TERM “REAGENT COMPARTMENT” AS A “REGION OR SECTION OF THE CONTAINMENT VESSEL”

A. The Intrinsic Record Confirms The Claims’ Plain Text, Which Places No Limit On The Location Of The “Reagent Compartment”

The default rule is that claim words carry “their ordinary and customary meaning.” *Poly-Am., L.P. v. API Indus., Inc.*, 839 F.3d 1131, 1136 (Fed. Cir. 2016). The Court has “recognized ‘only two exceptions to this general rule: 1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of a claim term either in the specification or during prosecution.’” *Unwired Planet, LLC v. Apple Inc.*, 829 F.3d 1353, 1358 (Fed. Cir. 2016) (citation omitted). This means that “[a] patentee is normally entitled to the full scope of its claim language.” *Duncan Parking Techs., Inc. v. IPS Grp., Inc.*, 914 F.3d 1347, 1364 (Fed. Cir. 2019). And claims should be construed to cover any embodiment that falls within their scope, regardless of whether that embodiment was described in the specification. *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371-72 (Fed. Cir. 2014). The mere fact that the specification might describe an invention one way “does not imply” that the claim is narrowed to only that way. *Duncan*, 914 F.3d at 1364.

These principles require giving the term “reagent compartment” its full scope: any compartment that contains a reagent. As the district court acknowledged

(Appx33), the claim text places no restriction on where the reagent compartment is located (what the district court called “ambiguous”). The only requirement the text imposes on the “reagent compartment” is that it have a barrier to hold and then release the “reagents into the sample receiving area.” Appx140 (col.19:45-48).

The claim text’s silence on where or how the reagent compartment must be positioned relative to other structures stands in contrast to the text’s treatment of other elements. Unlike for the reagent compartment, the claim specifies where and how other elements must physically relate to one another. For instance, the “containment vessel” must have an “opening for receiving a liquid sample and *for sealably receiving a sealing cap.*” Appx140 (col.19:39-40) (emphasis added). It also must have a marking “*on said one or more walls* which corresponds to a fluid volume in the sample receiving area.” Appx140 (col.19:43-44) (emphasis added). And the “reagents” must be located “*in the reagent compartment*” and separated by a barrier from the “sample.” Appx140 (col.19:45-49) (emphasis added). This language shows that the patentee added specific requirements when limiting how one claim element’s physical location related to another’s—requirements that are absent with respect to the “reagent compartment.” *See IGT v. Bally Gaming Int’l, Inc.*, 659 F.3d 1109, 1116-17 (Fed. Cir. 2011) (rejecting argument to “rewrite the claim” to add a limitation when other claim text showed that patentee knew how to

add such a limitation). There simply was no basis for the district court to rewrite the claim to add a location requirement for a claim element that didn't state or need one.

The specification confirms the claim text should carry its ordinary meaning without any limitation on where to locate the “reagent compartment.” The inventors provided no definition or express disclaimer for that term. Nothing in the specification states some advantage or benefit to placing the reagent compartment in the containment vessel, and the patent nowhere disparages or criticizes other places the reagent compartment might be placed. *Hill-Rom*, 755 F.3d at 1372. At most, the specification provides examples. But even those examples are not so narrowly confined to a “reagent compartment” within a “containment vessel.” One embodiment describes a “container” having two regions: one “for collecting a biological sample” and another for “containing a composition for preserving a nucleic acid.” Appx133 (col.6:28-31); Appx137 (col.14:51-53). And in the '398 provisional that the patent expressly “incorporated herein by reference in its entirety” (Appx131 (col.1:16-17)), another embodiment discloses a “compartment or compartments that contain the agent or agents” incorporated in “the underside of the cap of the container.” Appx3184; *see Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (provisional application incorporated by reference is “effectively part of the” specification as though it was “explicitly

contained therein”). At the very least, the provisional shows that nothing prevents the reagent compartment from being in the cap.⁵

Regardless, even if the embodiments in the patent pointed only in one direction, that still would not justify limiting the patent to a “reagent compartment” located in the “containment vessel.” *See Duncan*, 914 F.3d at 1364. Indeed, the patent expressly rejects such a narrow reading of the specification and the claims. It states that “the detailed description and the specific examples, while indicating preferred embodiments of the invention are given by way of illustration only,” and that changes and modifications to those examples fall within the “scope of the invention.” Appx134 (col.7:64-col.8:3); *see Pfizer, Inc. v. Ranbaxy Lab’ys Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006) (explaining that similar non-limiting language undermines argument that claims are limited to specific examples in the specification).

Cases like *Unwired Planet* confirm that claim text like that here carries its broad plain meaning. The district court there construed “voice input” to require that a voice input be transmitted over a dedicated voice channel as opposed to being

⁵ One embodiment from the provisional discloses the reagent compartment as a “small bag” in the cap. Appx3186. The issued patent discloses reagents being stored in a “bag compartment” even though no embodiments—other than the one with the reagent compartment in the cap—has reagents stored in a bag. Appx138 (col.15:17-20). This further demonstrates that the inventors intended the claims to carry their plain meaning with no limit on where or how the reagents might be stored.

transmitted over any data channel. *Unwired Planet*, 839 F.3d at 1356-57. This Court disagreed, explaining that “[b]y its plain language, the term ‘voice input’ does not dictate the manner in which voice is to be transmitted from a mobile device to a server.” *Id.* at 1358. The Court further explained that it was “undisputed that a voice input signal could be transmitted over either a voice channel or a data channel.” *Id.* Because nothing in the specification required departing from the claim text’s plain meaning, this Court reversed the district court’s construction.

The same reasoning requires the same result here. Like “voice input” in *Unwired Planet*, the plain meaning of “reagent compartment” does “not dictate” where the reagent compartment is located. Nor is there any dispute that a reagent compartment could be located in various places within the claimed device. In fact, the specification itself, either directly or through incorporation, identifies multiple locations for a reagent compartment—including in the cap—which reinforces that “reagent compartment” should take its plain meaning.

B. No Evidence Supports The District Court’s Conclusion That Genotek Disclaimed The Ordinary and Customary Meaning of “Reagent Compartment”

Despite the claim language placing no limit on where the reagent compartment is located within the claimed device, the district court concluded that Genotek had disclaimed the term’s ordinary and customary meaning. The district

court thus rewrote “reagent compartment” as a “region or section of the containment vessel.” Nothing the district court identified supports that result.

1. Specification passages stating what, “[d]esirably, the invention features” and the like contain no disclaimer

The primary basis for the district court’s disclaimer conclusion was two passages in the specification that described embodiments with “a container that has a first region for collecting a biological sample and a second region containing a composition for preserving a nucleic acid.” Appx133 (col.6:26-32, col.14:51-53). The first of those passages comes from a paragraph that begins: “In a sixth aspect, the invention features a device” Appx133 (col.6:26-32). The second is from a paragraph beginning: “Desirably, the invention features a device” Appx137 (col.14:49-51). Simply because those paragraphs begin with the phrase “the invention features,” the district court concluded that the passages describing a container with a region for preserving a nucleic acid were “a clear disclaimer that . . . the reagent compartment is in the container of the device and not in alternative locations.” Appx35-37.

That was error. To start, the district court ignored that the standard for disclaimer is “exacting,” and requires “clear and unmistakable statements by the patentee that limit the claims.” *Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1353 (Fed. Cir. 2016). “To disavow claim scope, the specification must contain expressions of manifest exclusion or restriction.” *Cont’l Cirs. LLC v. Intel*

Corp., 915 F.3d 788, 797 (Fed. Cir. 2019) (quotation marks omitted). It is “not enough that the only embodiments, or all of the embodiments, contain a particular limitation.” *Thorner v. Sony Comput. Ent. Am. LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012).

Consistent with these principles, this Court has rejected attempts to narrow claim terms to specific embodiments—even when the patent uses the phrase “the present invention” or similar phrases to describe those embodiments. Thus, in *Unwired Planet*, this Court rejected the district court’s disclaimer conclusion, which was based on a specification paragraph that began with “[t]he present invention relates to.” 829 F.3d at 1357-59. The Court dismissed the notion that everything in the paragraph that followed that phrase “constitutes a mandatory claim limitation to be read into the claims.” *Id.* at 1358.

Other decisions are in accord. In *Hill-Rom*, the Court reversed a construction limiting the term “datalink” to wired connections, instead holding that the term included both wired and wireless connections. 755 F.3d at 1371. In so doing, the Court “expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment.” *Id.* (citation omitted). In addressing another term, the Court also rejected the notion that the phrase “the present invention” limited a claim to a particular feature. It explained that “[t]he specification contain[ed] no discussion of

the importance, essentiality, or criticality of” that feature. *Id.* at 1377. And in *Continental Circuits v. Intel Corp.*, the Court reached a similar conclusion. There, the specification described a “repeated desmear process” as a feature of “the present invention.” 915 F.3d at 798. Yet this did not permit limiting the claim to that feature, because in other “portions of the specification” the invention was “described . . . without any requirement that the invention must encompass the repeated desmear process.” *Id.*

The parts of the specification the district court relied on here fall far short of disclaimer for similar reasons. They do not define the scope of the “reagent compartment” in any way, such as by dictating what a reagent compartment is or does. Indeed, they do not use the term “reagent compartment” at all. They merely show various options for how different embodiments might be configured. Appx133 (col.6:26-32); Appx137 (col.14:51-53, col.15:17-20); Appx1495; Appx1499. By relying on these statements to impose a location requirement on “reagent compartment,” the district court was not “clarify[ing] or constru[ing] the actual words of the claim”; it was creating an additional claim requirement. *Rambus Inc. v. Infineon Techs. Ag*, 318 F.3d 1081, 1089 (Fed. Cir. 2003). For the same reasons, the specification’s use of the phrase “the invention features” (Appx33-34) when describing certain embodiments, without more, fails to justify the district court’s

revision of the claims. *Unwired Planet*, 829 F.3d at 1358-59; *Hill-Rom*, 755 F.3d at 1376.

No decision the district court cited suggests otherwise. In *Techtronic Industries Co. v. International Trade Commission*, for example, this Court held that the term “wall console” was limited to wall consoles containing a “passive infrared detector.” 944 F.3d 901, 910 (Fed. Cir. 2019). But the Court did not reach that conclusion simply because the specification used the term only one way in conjunction with the phrase “the present invention.” *Id.* at 907. It did so because the specification disclosed “a wall console with a passive infrared detector as the critical and inventive feature” over the prior art. *Id.* at 910. Here, nothing in the specification suggests that the *location* of the reagent compartment is “the critical and inventive feature” of the reagent compartment. Of course, the specification does disclose inventive features, like a barrier to contain the reagent and a way to disturb the integrity of that barrier. Appx137 (col.14:31-37). But the patent claims those

features. Appx140 (col.19:43-48) (requiring a “barrier . . . capable of disestablishment”).⁶

2. *The omission of the provisional application’s embodiment fails to justify disclaimer*

The district court concluded that disclaimer was further supported by the specification’s *omission* of an embodiment found in the ’398 provisional. Appx38. The Court should reject that backwards reasoning. For one, there was no omission. The ’187 patent did not merely cite the provisional—the provisional was “incorporated herein by reference in its entirety.” Appx131 (col.1:19). *Advanced Display Sys., Inc.*, 212 F.3d at 1282 (provisional applications incorporated by

⁶ The district court’s reliance on other cases similarly fails. Appx34. In *Luminara*, the Court held that a “specification disclaim[ed] non-chaotic pivoting” when it explained that the invention’s feature of “chaotic” movements “solve[d] the problems associated with the prior art.” 814 F.3d at 1353-54. In *Pacing Technologies, LLC v. Garmin International, Inc.*, the Court held that an invention required a certain system when the specification explained that “the invention accomplishes *all* of its objects and features . . . with” that system. 778 F.3d 1021, 1025 (Fed. Cir. 2015). In *Honeywell International, Inc. v. ITT Industries, Inc.*, the Court held that “the claim term ‘fuel injection system component’ [was] limited to a fuel filter” when the specification referred to a fuel filter as “the present invention” four times and contained a “detailed discussion of” a “prior art problem” regarding fuel filters, which was “addressed by the patented invention.” 452 F.3d 1312, 1318 (Fed. Cir. 2006). And in *Poly-America, L.P. v. API Industries, Inc.*, the Court held that an invention was limited to a certain feature when “the specification indicate[d] the importance of” that feature in “every section” and “distinguish[ed] or disparage[d] prior art based on the absence of that feature,” and when the prosecution history indicated that the patentee distinguished the invention from prior art based on that feature. 839 F.3d 1131, 1135-37 (Fed. Cir. 2016).

reference are “effectively part of the” specification as though it was “explicitly contained therein.”). Under the district court’s reasoning, however, *nothing* from the provisional that is not expressly repeated in the ’187 patent’s specification was incorporated, and anything omitted from the issued patent was instead disclaimed.

None of the cases the district court cited supports such a categorical rule. *Contra* Appx39. The district court primarily relied on *MPHJ Technology Investments, LLC v. Ricoh Americas Corp.* Appx39 (citing 847 F.3d 1363 (Fed. Cir. 2017)). But the Court in *MPHJ* rejected a disclaimer argument—the opposite conclusion of the one the district court reached here. 847 F.3d at 1367-69. The patentee there argued for importing into the claims a “single-step operation” based on a limiting statement found only in a provisional application. *Id.* This Court disagreed, holding that the limiting statement was not a clear and unmistakable disclaimer, particularly because the patent “in its final form” described “the single-step operation as ‘optional.’” *Id.* The omission of the provisional’s limiting statement “contribute[d] understanding of the intended scope of the final application” because it “accord[ed] with” the final application’s express statement of optionality. *Id.* That is, the provisional’s limiting statement otherwise would have conflicted with the final patent’s statement that the single-step operation was optional, and the applicant resolved that conflict by removing the limiting statement. *See also Finjan LLC v. ESET, LLC*, 51 F.4th 1377, 1381-83 (Fed. Cir. 2022)

(specification’s broader definition of term “downloadable” governed rather than more restrictive and otherwise inconsistent definitions of “downloadable” found in earlier patent incorporated by reference).

The district court thus was wrong that *MPHJ*’s rejection of disclaimer somehow supports a conclusion of disclaimer here. In *MPHJ*—and unlike what the district court did here—the Court’s construction *included* the omitted embodiment from the provisional application involving a single-step operation; it just also included other embodiments. The Court in *MPHJ* also did not give significance to the mere omission of material from a provisional: it was the deletion of that material plus the inclusion of otherwise conflicting material in the issued patent “accord[ing] with the change” that mattered. 847 F.3d at 1369. No similar facts exist here. And of course, *MPHJ* was decided under the broadest reasonable interpretation standard (*id.* at 1364), which meant the Court *had to* adopt the broader construction when faced with two reasonable but competing alternatives—the narrower statement from the provisional or the broader “optional” language from the specification. This case is governed by the *Phillips* standard, which compelled the district court to adopt the claims’ ordinary and customary meaning absent a clear and unmistakable disclaimer.

3. *The district court erred in relying on extrinsic evidence and in interpreting that evidence*

The district court also improperly relied on extrinsic evidence for its narrowing construction: a description Genotek gave during an IPR of an unrelated

patent about an embodiment in the ancestral patent application to the '187 patent. In that IPR, the ancestral application, Birnboim, was asserted as prior art against an unrelated Genotek patent. Appx1550-1565. The petitioner had argued that Birnboim's "preferred embodiment" or "primary embodiment" suffered from a problem that would have led one of skill in the art to modify it with elements from another reference. Appx1550-1565 (quoting petition). Genotek had explained in response that the petitioner misinterpreted Birnboim, which describes "a rotated screw cap with a ram in the cap and a reagent below a plastic cover *in a container.*" Appx41 (emphasis added) (quoting Appx1562-1563). According to the district court, this statement confirmed that the claimed "reagent compartment" in the '187 patent must be in the "container."

Not so. In *Pfizer*, this Court held that "statements made during prosecution of the later, unrelated" patent "cannot be used to interpret claims of the" earlier patent. *Pfizer*, 457 F.3d at 1290. Since then, the Court has reiterated that "statements made" on "unrelated applications" are "not relevant to claim construction." *Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1312 (Fed. Cir. 2014), *overruled on other grounds by Williamson v. Citrix Online, LLC*, 792 F.3d 1339 (Fed. Cir. 2015). And it has subsequently confirmed that there is "no reason to question the rule in *Pfizer*." *Hill-Rom*, 755 F.3d at 1381. In bypassing this rule, the district court made no attempt to distinguish this precedent. Instead, it relied on other decisions treating statements

made during patent prosecution as “relevant.” Appx42. But those cases all involved statements made in proceedings for *related* patents in the same family, or in proceedings for the underlying patent itself (and in one instance, statements made in the patent, not during prosecution at all). *See Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1349 (Fed. Cir. 2004) (discussing statements in related-patent prosecutions and rejecting disclaimer based on those statements); *Honeywell Int’l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1318 (Fed. Cir. 2006) (discussing statements in the patent itself, not during prosecution); *Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1359 (Fed. Cir. 2017) (discussing statements made in a patent’s prosecution history); *A.G. Design & Assocs. LLC v. Trainman Lantern Co.*, 271 F. App’x 995, 998 n.4 (Fed. Cir. 2008) (discussing interpreting claims consistently for both validity and infringement analyses for the same patent).

Regardless, the district court misread the statement from the unrelated IPR. It interpreted the statement as describing the invention “as a whole,” and rejected Genotek’s argument that the statement described an embodiment only. Appx41 n.20. That is quickly disproven. The obviousness challenge Genotek was responding to in the IPR was that “the preferred embodiment exemplified in Birnboim had readily recognizable problems,” which the petitioner asserted would have led to modifications using another reference. Appx1552-1553. Genotek’s statement explained why persons of ordinary skill in the art would not have made

the proposed changes to that preferred embodiment, because “O’Donovan [the other reference] and Birnboim are very different devices.” Appx1562-1563. Genotek stated that Birnboim has “a reagent below *a plastic cover* in a container.” Appx1562-1563 (emphasis added). In other portions of its IPR brief, Genotek described that plastic cover as merely one embodiment of Birnboim. Appx1556-1557. Regardless, the ’187 patent never even uses the phrase “plastic cover”—much less equate “plastic cover” to “reagent compartment” or limit the location of any such feature. Nothing, then, about Genotek’s description of a preferred embodiment in the IPR disclaimed anything about the “reagent compartment” later claimed in the ’187 patent.

In any event, there is no indication that Genotek’s use of the word “container” in the IPR brief—or in the ’187 patent generally—described only the “containment vessel” that the claim recites. To the extent the district court’s conclusion necessarily follows from its daisy-chaining of its own construction of “containment vessel” to mean “container,” that would mean its construction of “containment vessel” was wrong too. Appx21. After all, some portions of the specification clearly understand the word “container,” as used in the specification, to have a broader meaning than “containment vessel.” For example, the specification describes “desirable features of this collection vessel” or “container” as “includ[ing],” among other things, a “means for closing the container” such as “a cap.” Appx137

(col.14:61-15:32). And it describes Figures 10 and 11 as exploded views of the “sample container of the invention”; that figure includes “cap 1.” Appx134 (col.8:46-47, col.15:33-34). Yet according to the district court, the claimed containment vessel excludes the cap. Appx87-91. The mere fact that “containment vessel” may mean “container” should not mean that every reference to “container” in the specification necessarily means “containment vessel.”

Because there is no possibility that the IPR statement was describing the full scope of the invention, it says nothing about disclaimer—even if a statement made in an unrelated patent’s IPR were somehow relevant to claim construction.

C. Vacatur Is Required Because Spectrum’s Products Have A “Reagent Compartment” Under The Correct Construction

Had the district court properly construed the term “reagent compartment,” it could not have granted Spectrum summary judgment of noninfringement on the ’187 patent. The record evidence shows that, if the “reagent compartment” can be somewhere other than the “containment vessel,” at least disputes of fact exist over whether Spectrum’s products have a “reagent compartment”: it was undisputed at summary judgment that “the cap of” of Spectrum’s accused products “includes a compartment containing a reagent solution.” Appx4464.

Nor does it matter that the district court said it had granted summary judgment based on a different limitation—the purported absence of a “containment vessel” in Spectrum’s products. Appx91-92. That is because the district court’s containment

vessel conclusion cannot be separated from its construction of “reagent compartment.” In granting summary judgment, the district court addressed Genotek’s *amended* infringement contentions, which were changed in response to the district court’s construction. In those amended contentions, Genotek asserted that the “containment vessel” could include the sealing cap, which was where the reagent compartment is found in Spectrum’s products. Appx 3615; Appx3640. In addressing those amended contentions, the district court determined that a container with a cap could not be a “containment vessel.” Appx91-92.

Under Genotek’s original infringement contentions, however, Spectrum’s container without a cap met the requirements of the “containment vessel having a top having an opening” limitation—something Spectrum did not dispute when it moved for summary judgment. Appx4464-4465; Appx5788-5789 (Spectrum “conced[ing]” at summary-judgment hearing that its product did “have a containment vessel”); Appx306. So once the district court’s construction of “reagent compartment” is reversed, the sole basis for its grant of summary judgment on the ’187 patent no longer exists.

II. FOR THE ’646 PATENT, THE DISTRICT COURT ERRED IN ITS CONSTRUCTION OF “PRESERVING A BIOLOGICAL SAMPLE”

In construing the term “preserving a biological sample,” the district court made two independent errors. First, it turned a statement of purpose and intended use from the preamble of an apparatus claim into a functional claim requirement that

the apparatus must achieve a certain result. Second, even if the preamble imposes a claim requirement, the district court narrowly construed the term absent any disclaimer of the term's ordinary and customary meaning.

A. The Court Erred In Determining That The Preamble Is Limiting

1. *The body of the apparatus claim recites a structurally complete invention and the preamble states only an intended purpose or use*

This Court has held that “as a general rule preamble language is not treated as limiting.” *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335, 1347 (Fed. Cir. 2012). And it has repeatedly explained that “a preamble is not limiting where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.” *Cochlear Bone Anchored Solutions AB v. Oticon Med. AB*, 958 F.3d 1348, 1355 (Fed. Cir. 2020) (quoting *Arctic Cat Inc. v. GEP Power Prods., Inc.*, 919 F.3d 1320, 1328 (Fed. Cir. 2019)). This is particularly true for apparatus claims, which “cover what a device *is*, not what a device *does*.” *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1468 (Fed. Cir. 1990) (emphasis by court). For that reason, “preambles describing the use of an invention generally do not limit the claims because the patentability of apparatus or composition claims depends on the claimed structure, not on the use or purpose of that structure.” *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002).

Artic Cat is instructive. There, the preamble to the claimed power distribution module “identifie[d] an intended use”—“for a personal recreation vehicle.” 919 F.3d at 1328.⁷ The Court deemed this intended use non-limiting because it did not “impose[] any structural requirement on the claimed module beyond what is required by the bodies of the claims” and there was no “reliance on the preamble . . . to distinguish the claimed invention from the prior art.” *Id.*

In *Cochlear Bone*, the preamble similarly identified an intended use: “for rehabilitation of unilateral hearing loss.” 958 F.3d at 1355. The Court concluded this statement was “merely a statement of intended use of the claimed hearing aid” and that it “identifie[d] no structure for the apparatus claimed.” *Id.* And it noted that “[t]he bodies of the claims contain the only descriptions of the structure for the hearing aid, with no additional structure furnished by the preamble phrase at issue.” *Id.*⁸

So too here. The ’646 patent’s preamble states a “purpose” and “intended use” for the claimed apparatus: “for collecting and preserving a biological

⁷ The Court explained that it made no difference whether the broadest reasonable interpretation or *Phillips* standard applied in that case. 919 F.3d at 1328.

⁸ Although this case was decided under the broadest reasonable interpretation standard, the Court relied on cases decided under the *Phillips* standard, and, as in *Artic Cat*, there is no indication that it would have been “reasonable” to construe the preamble as limiting.

sample. . .” Appx183 (col.22:16-17). The body of the claim sets forth the structures of the claimed “kit.” These structures include: “a sample collection vessel,” “a cap,” and “a movable annular valve.” Appx183 (col.22:18-47). The claim recites specific requirements for each structure, such as a reservoir for the sample collection vessel, a reagent chamber in the cap for storing a reagent, and “connection member[s]” in each configured to engage with each other. Appx183 (col.22:18-30). And the “moveable annular valve” has several requirements, including an inner cylinder, an outer cylinder, an aperture, and interior sidewall—each with their own requirements. Appx183 (col.22:31-47). These requirements recite “a structurally complete invention.” *Catalina*, 289 F.3d at 810. The preamble, in contrast, merely states *how* and *why* the apparatus may be used, without reciting any “additional structure or steps” of the invention. *Id.* at 808.

The specification confirms that the claim body recites the “essential structure” of the claimed kit—and that the preamble’s statement of use/intended purpose states no structure, or anything else, essential to understanding the claimed device. *Id.* (preamble may be limiting when inventors relied on it to “define the claimed invention”). For instance, the specification discloses that “in some embodiments, the sample collection devices use a minimum amount of parts” (Appx174 (col.4:64-66)), which can include “two main mating bodies, a cap and a tube,” with the “cap . . . includ[ing] a closed cavity holding a preservative solution” (Appx175 (col.5:12-

13)). *See also* Appx174-175 (col.4:62-6:21); Appx177-180 (col.10:3-16:8) (portions of the detailed description of the embodiments discussing the device). Claim 1 expressly recites structures like those recited in the specification, reinforcing that the claim recites a structurally complete invention. Appx183 (col.16-47). And none of those portions of the specification discusses preserving a biological sample, other than noting that the device can be used for preserving fluids. Appx178 (col.12:38); Appx179 (col.13:46, col.14:34, col.14:47); Appx180 (col.15:5). The absence of any such discussion reinforces that the preamble’s statement of intended purpose is *not* essential to the claimed apparatus and imparts no additional essential structure.

To be sure, some specification passages discuss preserving cells (though not “preserving a biological sample”) in more detail, but those statements relate to embodiments not claimed by the ’646 patent: solutions and methods for preserving cells. *E.g.*, Appx180 (col.16:9); Appx181 (col.17:30-31). It is well-settled that “a claim need not cover all embodiments,” because “[a] patentee may draft different claims to cover different embodiments.” *Intamin Ltd. v. Magnetar Techs., Corp.*, 483 F.3d 1328, 1337 (Fed. Cir. 2007); *see TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008) (noting many instances where “subject matter . . . is included in the specification, but is not claimed”). Here, the specification expressly distinguishes between embodiments relating to sample

collection *devices* (what the '646 patent claims) and embodiments relating to a *solution* or *method* of preserving biological samples (which the '646 patent does not claim). As the specification explains, “[e]mbodiments of the disclosure provide safer and easy to use sample collection devices for naturally expressed bodily fluids (for example), *as well as* solutions and methods for preserving cells of samples collected, *and additionally*, methods for isolating specific cells either collected and/or preserved.” Appx174 (col.4:53-58) (emphases added). The embodiments of unclaimed solutions and methods thus cannot support treating the preamble as limiting.

2. *The district court’s antecedent-based rationale fails*

The district court’s sole ground for concluding the preamble was limiting was that the preamble’s “*a biological sample*” provides the antecedent basis for the claim body phrase “*the biological sample*.” Appx61. Yet this Court has explained that a preamble is limiting on this basis only if it “provide[s] antecedent basis for and [is] necessary to understand positive limitations in the body of claims.” *Pacing Techs., LLC v. Garmin Int’l, Inc.*, 778 F.3d 1021, 1024 (Fed. Cir. 2015). This means that the claim must show that the patentee relied on “*both* the preamble and the body to define the subject matter of the claimed invention.” *Bell Commc’ns Rsch., Inc. v. Vitalink Commc’ns Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995) (emphasis by court). Otherwise, a preamble would be limiting whenever it contained a phrase that

reappeared in the claim body. *Catalina*, 289 F.3d at 808 (rejecting such a “litmus test”).

The district court’s construction exemplifies this error. It located antecedent language but never asked whether that language—“a biological sample”—defined any part of the invention. For good reason: nothing about the preamble’s initial use of “a biological sample” defines or explains what that biological sample is. And none of the claimed apparatus’s structures, such as the “collection vessel,” the “collection reservoir” with an “opening configured to receive the biological sample,” or the “connection member” (Appx187 (col.22:20-25)), depends on how the preamble describes “a biological sample”—even if the preamble had said more.

This Court addressed similar issues in *American Medical Systems, Inc. v. Biolitec, Inc.*, 618 F.3d 1354 (Fed. Cir. 2010). There, the Court held that “the preamble term ‘photoselective vaporization of tissue’ d[id] not provide a necessary antecedent basis for the term ‘the tissue’ in the bodies of each of the independent claims.” *Id.* at 1359. That was because “the claim drafters did not rely on the preamble language to define or refine the scope of the asserted claims”: the preamble’s reference to tissue “d[id] not specify a particular type or location of tissue being treated”; nor did that “generic term . . . provide any context essential to understand[ing] the meaning of ‘the tissue’ in the body of each claim.” *Id.* (alterations in original).

The conclusion that the preamble is nonlimiting is even stronger here. As in *Biolitec*, the preamble's mere reference to "a biological sample" in no way "define[s] or refine[s] the scope of the asserted claims." *Id.* The preamble "specif[ies]" nothing about the biological sample nor "provide[s] any context" essential to understanding its meaning in the claim body. *Id.* (quotation marks omitted). Those facts were enough to render the preamble nonlimiting in *Biolitec* even though the claim there was a method claim and actually covered how a laser radiation device was used to treat tissue. *Id.* The similar facts here are all the more sufficient to render the preamble nonlimiting for the apparatus claim, which covers what the apparatus is, not what it does with a biological sample. *See Hewlett-Packard*, 909 F.2d at 1468.

Regardless, even if "a biological sample" provided a necessary and limiting antecedent basis for "the biological sample," the district court's decision to deem the preamble's broader phrase—"preserving a biological sample"—limiting still could not be justified. A "conclusion that some preamble language is limiting does not imply that other preamble language, or the entire preamble, is limiting." *Cochlear Bone*, 958 F.3d at 1355; *see TomTom, Inc. v. Adolph*, 790 F.3d 1315, 1322-24 (Fed. Cir. 2015) (concluding that structural requirements in the preamble were limiting while statements of "purpose or intended use" in the preamble were not). Here, "preserving" provides no antecedent basis for any part of the body of the claim. The claim body never uses the word "preserving" or refers to preservation: it merely

recites structures. Appx187 (col.22:16-21). Nor is “preserving” necessary to understand the body of the claims, for all the reasons stated above. *Supra* pp. 41-44. To take just one example, nothing about the requirement that the annular valve’s “aperture accommodates at least a portion of the inner cylinder” depends on the concept of preservation. Appx187 (col.22:31-44).

The district court did not disagree; indeed, it did not conclude that the word “preserving” was limiting at all. It instead found that this Court’s decision in *Bio-Rad Laboratories, Inc. v. 10X Genomics Inc.*, 967 F.3d 1353 (Fed. Cir. 2020), required treating an entire preamble as limiting under these circumstances. Appx61. The district court misapprehended *Bio-Rad*. The claim in *Bio-Rad* was for a *method*, and the preamble recited “[a] method for conducting a reaction in plugs in a microfluidic system.” 967 F.3d at 1361. Having deemed the specific terms “reaction” and “microfluidic systems” limiting, the Court concluded those terms were “intertwined” with the entire preamble, such that they could not “be read separately from the remainder of the preamble.” *Id.* at 1371. In particular, the preamble indicated that the inventors intended to limit the claimed methods to certain types of “reactions.” *Id.* None of those concerns apply to the ’646 patent’s claims, which are directed only to an apparatus.

B. In Any Event, The District Court Erred In Its Construction of “Preserving A Biological Sample”

Even if the entire preamble is limiting, the district court improperly narrowed the term “preserving a biological sample” to “preventing cells in the biological sample from having their antigens degraded such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome.” Appx59.

1. “Preserving a biological sample” is broader than the functional result of preserving cells through the specific measures the district court required

The claim text, specification, and extrinsic evidence confirm that “preserving a biological sample” would have its ordinary and customary meaning to persons of ordinary skill in the art—slowing degradation of a biological sample.

Start with what the claim itself says about “biological sample.” Very little, and nothing that supports the district court’s construction. The claim requires no physical characteristic of the biological sample; it can be anything “receive[d] . . . from a user.” Appx183 (col.22:20-22). And based on the preamble, it must be capable of being collected and preserved. Genotek was thus entitled to the “full scope” of that claim term. *Duncan*, 914 F.3d at 1364. Assuming that the functional requirement “preserving a biological sample” in the preamble is limiting, the district court should have construed that term to mean preserving any biological material intended to be collected from a user.

The claim text similarly imposes no limitations on “preserving.” Nothing in the preamble states to what extent or degree the biological material must be preserved, for how long, how the preservation should be accomplished, or what results are required for preservation to have occurred. Thus, “based on the plain language,” the claim is “not limited to a” particular mode of preservation or to particular results that must be achieved through that preservation. *Cont’l Cirs.*, 915 F.3d at 796.

The specification also offers no basis to further limit “preserving a biological sample.” Indeed, it never uses the phrase “preserving a biological sample” at all. Instead, in some places, the specification discusses preserving one type of biological sample: cells. But these passages describe embodiments of the *solutions* and *methods* that the patent discloses—not the kit that the patent here claims. *E.g.*, Appx174 (col.4:53-56) (“Embodiments of the disclosure provide . . . solutions and methods for preserving cells of samples collected.”); Appx175 (col.6:54-55) (“[S]ome embodiments of the disclosure include methods for preserving the antigenicity and epigenome of cells.”); Appx175 (col.6:61-63) (“[I]n some embodiments, a solution for preserving cells in bodily fluids . . . is provided.”); Appx180 (col.17:30-31) (“In some embodiments of the disclosure, a method for preserving cells in one or more bodily fluids is disclosed.”).

Where the specification discloses embodiments relevant to what the '646 patent claims, it discusses the collection of bodily fluids, not just cells. For instance, some “[e]mbodiments of the disclosure provide safer and easy to use sample collection devices for naturally expressed bodily fluids (for example)” (Appx174 (col.4:53-55)), and in other “embodiments, a bodily fluid sample collection device for the collection of naturally expressed bodily fluid is provided,” (Appx175 (col.6:6-8)).

Finally, extrinsic evidence shows that preserving a biological sample would not be understood to mean only preserving cells. Dr. Michael Metzger explained that an ordinary artisan “would have understood the term ‘preserving a biological sample’ to mean ‘slowing degradation of a biological sample.’” Appx2836. And he stated that “a biological sample of the '646 Patent” could be “a cell-free plasma sample that contains either cell-free fetal DNA (‘cffDNA’) obtained from the blood of a pregnant mother or cell-free circulating tumor DNA (‘ctDNA’) obtained from the blood of a cancer patient.” Appx2837 (emphasis omitted); *see* Appx2553-2554; Appx2559; Appx2563 (also discussing cell-free urine). Spectrum never contested these statements.

2. The intrinsic record fails to support the district court’s construction

The district court justified its contrary construction based on the specification’s statements that “[t]he disclosure relates to devices, solutions and

methods for collecting and processing samples of bodily fluids containing cells” and that “the disclosure relates generally” to, among other things, “the isolation and preservation of cells.” Appx62-63 (quoting Appx173 (col.1:21-27)). And it observed that “the specification never references any type of preservation other than the preservation of cells.” Appx64. From there, the district court took an express definition of another term not found in the claims—“preserving cells”—and imported the specification’s statements about preserving cells into the preamble’s “preserving a biological sample.”

But merely stating that a disclosure “relates generally” to “the isolation and preservation of cells” hardly signals an invention-defining requirement, absent an indication that preserving cells is an essential feature of the claimed apparatus. *Unwired Planet*, 829 F.3d at 1358-59; *Hill-Rom*, 755 F.3d at 1376. And again, these embodiments disclose “solutions” and “methods,” neither of which are claimed by the ’646 patent. Appx58. Nor was the district court correct that all the disclosures discuss preserving *cells*. Appx58. Several disclosures state that a biological sample may be any “bodily fluid.” *E.g.*, Appx174 (col.4:53-55); Appx175 (col.6:6-8). And Dr. Metzker testified—and Spectrum did not contest—that a person of ordinary skill would know that not all “bodily fluid[s]” contain cells. *See* Appx2552-2554; Appx2559; Appx2563 (Dr. Metzker opining that urine can be cell-free, discussing applications for “using a bodily fluid that does not require cells,” and stating that “a

biological sample can contain cells, but a biological sample also can also not contain cells”); Appx2837 (similar). In any event, even if the disclosures only discussed cells, that still would not justify narrowing the claims to what those specific embodiments disclose. *Thorner*, 669 F.3d at 1366 (noting that it is “not enough” to narrow claims “that the only embodiments, or all of the embodiments” have a particular feature).

Setting aside those errors, the district court made yet another mistake: it took the definition for “preserving cells” and imported it wholesale into the definition for “preserving a biological sample.” Appx64-65. The specification states: “For purposes of the disclosure, ‘preserving cells’ means preventing the cells from having their antigens degraded, such that they can be purified or enriched based on their antigens, and preventing alternations in the cellular epigenome.” Appx180 (col.16:23-27). Had the inventors intended all those functional requirements to apply to the apparatus claims here, they certainly would have used or incorporated the term “preserving cells,” rather than “preserving a biological sample.” It’s one thing for a patentee to act as its own lexicographer; it’s another where—as here—the district court assumes the role of the lexicographer by choosing words that fit within an express definition of *another term*.

The district court’s grant of summary judgment exposes the problems with that approach. In concluding that there was no genuine dispute over whether

Spectrum had infringed the apparatus claims, the district court identified no structural difference between Spectrum's products and the claimed apparatus. Appx103-113. The district court's entire analysis focused on how Spectrum's products are used—whether those “products preserve cells of a biological sample” under the district court's elaborate construction. Appx103-113. The district court's rewriting of Genotek's apparatus claims thus wrongly turned them into method claims, contrary to long-settled law. *Hewlett-Packard*, 909 F.2d at 1468.

The summary judgment order also reveals another flaw in the district court's construction: it put a further gloss on its functional construction of the term “preserving a biological sample.” Although Genotek produced evidence that Spectrum's products preserved one kind of antigen (TLR2 antigens), the district court granted summary judgment anyway. It concluded that Genotek needed to show that *all other* types of antigens in the sample were similarly preserved—regardless of whether the user intended to preserve those particular antigens. Appx107-108. No intrinsic or extrinsic evidence supports such a restrictive interpretation. The specification states only that preserving cells means preventing those cells “from having their antigens degraded.” Appx180 (col.16:23-27). By its express terms, that statement has no floor—all it requires is *some* antigens in a sample be protected from degradation.

The district court similarly went astray in determining what “preventing alterations in the cellular epigenome” requires. It rejected Genotek’s evidence as insufficient because it did not measure for “acetylation of lysine residues of histones,” a type of change to proteins associated with DNA. Appx111-112. But the district court’s construction—based on the functional definition of the term “preserving cells”—says nothing about the prevention of acetylation. Instead, the district court relied on yet another single sentence in the specification, which states that “[e]xamples of such alteration include methylation at the 5 position of cytosine in a CpG dinucleotide, acetylation of lysine residues of histones, and other heritable or non-heritable changes that do not result from changes in the underlying DNA sequence.” Appx112; Appx180 (col.16:29-31). But providing various *examples* of “alterations in the cellular epigenome” is not equivalent to saying that the only way to prove prevention of alteration is by measuring each of those examples.⁹

⁹ In fact, taking the district court’s reasoning to its logical conclusion would mean Genotek could not show that Spectrum’s solution prevented alteration of the cellular epigenome unless Genotek showed the absence of *any* “heritable or non-heritable changes”—an interpretation the district court appeared to endorse by concluding Genotek would need to prove absence of methylation and absence of acetylation “at the very least.” Appx111-113.

C. This Court Should Vacate The District Court’s Grant Of Summary Judgment

Once the district court’s erroneous construction is set aside, this Court should vacate the grant of summary judgment on the ’646 patent. The district ruled that Genotek had not shown Spectrum’s products meet the limitation “preserving a biological sample.” Appx107-112. Yet under the correct construction, the preamble (or at least, its “preserving” portion) is not limiting. Even if it is, there is at least a genuine dispute of fact whether Spectrum’s products meet the “preserving a biological sample” limitation under the correct construction of that term, which does not require preserving cells. Finally, even if both those conclusions are supported, the district court improperly limited the term “preserving a biological sample” further at summary judgment, and found Genotek’s evidence of cell preservation insufficient based on that newly restrictive construction. These errors all independently require vacatur.

CONCLUSION

The district court’s claim construction and summary-judgment ruling should be vacated and remanded for further proceedings.

Dated: September 28, 2023

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ADDENDUM

DNA GENOTEK INC.

v.

SPECTRUM SOLUTIONS LLC

No. 23-2017 (Fed. Cir.)

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

DNA GENOTEK INC., a California
Corporation,

Plaintiff,

v.

SPECTRUM SOLUTIONS L.L.C., a Utah
Limited Liability Company,

Defendant.

Case No.: 3:21-CV-00516-RSH-DDL

ORDER:

**(1) CLAIM CONSTRUCTION
ORDER; AND**

**(2) DENYING AS MOOT
PLAINTIFF’S MOTION FOR
LEAVE TO FILE A RESPONSE TO
DEFENDANT’S EVIDENTIARY
OBJECTIONS**

[ECF No. 101.]

In this case, Plaintiff DNA Genotek (“DNA Genotek”) alleges that Spectrum Solutions L.L.C. (“Spectrum”) infringes U.S. Patent Nos. 10,619,187 (“the ’187 Patent”) and 11,002,646 (“the ’646 Patent”) (collectively “the patents-in-suit”). On January 7, 2022, the Parties filed their Joint Claim Construction Hearing Statement, Chart, and Worksheet in accordance with Patent Local Rule 4.2. ECF No. 74. On February 18, 2022, the Parties

1 filed their Opening Claim Construction Briefs. ECF Nos. 134, 147.¹ On March 4, 2022,
2 the Parties filed their Responsive Claim Construction Briefs. ECF Nos. 88, 89. On
3 November 9, 2022, the Court emailed counsel of record a tentative claim construction
4 order.

5 The Court held a claim construction hearing on Thursday, November 10, 2022. ECF
6 No. 176. After considering the parties' briefing and the arguments presented at the hearing,
7 the Court issues the following claim construction order.

8 **I. BACKGROUND**

9 DNA Genotek is the owner by assignment of the '187 Patent and the '646 Patent.
10 *See* U.S. Patent No. 10,619,187, at [73] (issued Apr. 14, 2020); U.S. Patent No. 11,002,646,
11 at [73] (issued May 11, 2021). In the present action, DNA Genotek alleges that Spectrum
12 infringes the patents-in-suit, either literally or under the doctrine of equivalents, by making,
13 using, offering for sale, selling and/or importing saliva DNA collection devices, including
14 Spectrum's SDNA-1000 and SDNA-2000 products. *See* SAC (Aug. 4, 2021), ECF No. 20
15 ¶¶ 3, 18, 22-27, 35-45, 55-65.

16 The patents-in-suit both generally relate to devices for biological sample collection.
17 The '187 Patent was issued on April 14, 2020 and is entitled "Compositions and Methods
18 for Obtaining Nucleic Acids from Sputum." '187 Patent at [54], [45]. The invention
19 disclosed in the '187 Patent "relates to compositions and methods for preserving nucleic
20 acids at room temperature for extended periods of time and for simplifying the isolation of
21 nucleic acids." *Id.* col. 1 ll. 23-26. Specifically, the invention "features a composition for
22 preserving nucleic acids that includes a chelating agent, and a denaturing agent, where the
23 pH of the composition is greater than 5.0." *Id.* col. 3 ll. 61-64.

24 Independent claim 1 of the '187 Patent, the only independent claim in the '187
25 Patent, claims:

26
27
28 ¹ On July 19, 2022, DNA Genotek filed a Corrected Opening Claim Construction
Brief. ECF No. 134.

1 1. A device for receiving and preserving nucleic acid in a biological sample,
2 said device comprising:

3 a. one or more walls defining a containment vessel having a top having an
4 opening, and a closed bottom having a sample receiving area for holding said
5 biological sample, said opening for receiving a liquid sample and for sealably
6 receiving a sealing cap, said top having an opening for receiving a biological
7 sample from the mouth of a user and further comprising at least one marking
8 on said one or more walls which corresponds to a fluid volume in the sample
9 receiving area;

10 b. a reagent compartment having a barrier, said barrier sealing and containing
11 reagents in said reagent compartment and capable of disestablishment to
12 release said reagents into the sample receiving area;

13 c. reagents in the reagent compartment for preserving nucleic acids potentially
14 present in the sample wherein said reagents comprise a denaturing agent, a
15 chelator and a buffer agent; and,

16 d. the sealing cap, whereby the device is configured such that, when sealably
17 closing said opening with said sealing cap, the barrier mechanically
18 disestablishes to release said reagents to form a mixture of reagents and said
19 biological sample wherein said buffering agent maintains a pH of said mixture
20 equal to or above 5.0 to preserve nucleic acids potentially present in the
21 sample.

22 '187 Patent col. 19 ll. 34-59.

23 The '646 Patent was issued on May 11, 2021 and is entitled "Devices, Solutions and
24 Methods for Sample Collection." '646 Patent at [54], [45]. The invention disclosed in the
25 '646 Patent generally relates to devices, solutions, and methods for collecting samples of
26 bodily fluids containing cells. *Id.* at [57], col. 1 ll. 21-24. The '646 Patent also generally
27 relates to the isolation and preservation of cells from such bodily fluids for cellular analysis.
28 *Id.* at [57], col. 1 ll. 24-29.

1 Independent claim 1 of the '646 Patent, the only independent claim in the '646
2 Patent, claims:

3 1. A kit for collecting and preserving a biological sample, the kit comprising:

4 a sample collection vessel, the sample collection vessel comprising:

5 a sample collection reservoir having an opening configured to receive
6 the biological sample from a user into the sample collection reservoir;

7 a connection member disposed on an exterior portion of the sample
8 collection vessel and adjacent to the opening;

9 a cap, the cap comprising:

10 a reagent chamber configured to store a reagent; and

11 a complementary connection member configured to engage the
12 connection member of the sample collection vessel; and

13 a movable annular valve configured to associate with the cap and with the
14 opening of the sample collection reservoir, the movable annular valve
15 comprising:

16 an inner cylinder in fluid-tight association with the cap and comprising
17 a sidewall, the sidewall comprising a fluid vent; and

18 an outer cylinder in fluid-tight association with the inner cylinder and
19 associated with the opening of the sample collection reservoir, the outer
20 cylinder comprising an aperture defined by an interior sidewall of the
21 outer cylinder,

22 wherein the aperture accommodates at least a portion of the inner
23 cylinder,

24 wherein the interior sidewall obstructs the fluid vent when the movable
25 annular valve is closed, and

26 wherein the interior sidewall does not obstruct the fluid vent when the
27 movable annular valve is open.

28 '646 Patent col. 22 ll. 16-47.

1 On March 24, 2021, DNA Genotek filed a complaint for patent infringement against
2 Spectrum, alleging infringement of the '187 Patent. *See* Compl. (Mar. 24, 2021), ECF No.
3 1. On June 8, 2021, DNA Genotek filed its Second Amended Complaint (the "SAC," the
4 operative complaint) against Spectrum, adding a claim for infringement of the '646 Patent.
5 *See* SAC (Aug. 4, 2021), ECF No. 20. On August 18, 2021, Spectrum filed an answer to
6 the SAC along with counterclaims against DNA Genotek for: (1) declaratory judgment of
7 non-infringement of the patents-in-suit; (2) declaratory judgment of invalidity of the
8 patents-in-suit; (3) declaratory judgment of unenforceability of the '187 Patent due to
9 inequitable conduct; (4) monopolization in violation of section 2 of the Sherman Act, 15
10 U.S.C. § 2; and (5) attempted monopolization in violation of section 2 of the Sherman Act,
11 15 U.S.C. § 2. *See* Answer & Counterclaims (Aug. 18, 2021), ECF No. 27.

12 On September 2, 2021, the Court issued a scheduling order for the action. ECF No.
13 29. On April 1, 2022, the Court denied DNA Genotek's motion to dismiss Spectrum's
14 counterclaims for inequitable conduct, monopolization, and attempted monopolization,
15 and the Court denied DNA Genotek's motion to strike Spectrum's affirmative defenses of
16 inequitable conduct, patent misuse, and unclean hands. ECF No. 111. On May 25, 2022,
17 the Court issued an amended scheduling order. ECF No. 130. By the present claim
18 construction charts, worksheets, and briefs, the Parties agree upon the proper construction
19 for two claim terms, and the Parties request that the Court construe eleven disputed claim
20 terms from the patents-in-suit. ECF Nos. 74-1, 74-2, 88, 89, 134, 147.

21 **II. PLAINTIFF'S MOTION FOR LEAVE TO FILE A RESPONSE TO** 22 **DEFENDANT'S EVIDENTIARY OBJECTIONS**

23 As an initial matter, the Court addresses DNA Genotek's motion for leave to file a
24 response to Defendant's Evidentiary Objections. Along with its responsive claim
25 construction brief, Spectrum filed a document entitled "Defendant's Evidentiary
26 Objections to the Declaration of Dr. Michael L. Metzker Filed in Support of DNA
27 Genotek's Opening Claim Construction Brief." ECF No. 88-1. In the filing, Spectrum
28 objects to portions of Dr. Metzker's declaration for failure to comply with the Court's

Patent Local Rules, specifically Patent Local Rules 4.1(b), 4.1(d), and 4.2(d)(2).² *Id.* at 1-3.

On March 21, 2022, DNA Genotek filed a motion for leave to file a response to Spectrum’s evidentiary objections. ECF No. 101. In the motion, DNA Genotek argues that Spectrum’s filing is improper and unauthorized because the filing of separate “evidentiary objections” is a state procedural device that is not envisioned by the Federal Rules of Civil Procedure or the Court’s Patent Local Rules. *Id.* at 1.

The Court declines to address Spectrum’s evidentiary objections. In the filing, Spectrum objects to certain portions of Dr. Metzker’s declaration, specifically, certain statements in paragraphs 18, 25, 34, 60, 63, and 67 of the declaration. *See* ECF No. 88-1 at 3-6. Although the Court is skeptical that these portions of Dr. Metzker’s declaration complied with Patent Local Rule 4.2(d)(2), the Court does not rely on or reference any of the statements at issue in reaching the claim constructions set forth below. Thus, because

² Patent Local Rule 4.1(b) provides: “Simultaneously with exchange of the ‘Preliminary Claim Constructions[,]’ . . . [w]ith respect to any such witness, percipient or expert, the parties must also provide a brief description of the substance of that witness’s proposed testimony.” S.D. Cal. Pat. L.R. 4.1(b). Similarly, Patent Local Rule 4.1(d) provides: “Simultaneously with exchange of the ‘Responsive Claim Constructions[,]’ . . . [w]ith respect to any such witness, percipient or expert, the parties must also provide a brief description of the substance of that witness’s proposed testimony.” *Id.* 4.1(d). Patent Local Rule 4.2(d)(2) further provides: “The Joint Hearing Statement must include: . . . [w]hether any party proposes to call one or more witnesses, including experts, at the Claim Construction Hearing, the identify of each such witness, and for each expert, a summary of each opinion to be offered in sufficient detail to permit a meaningful deposition of that expert.” *Id.* 4.2(d).

“A district court has wide discretion in enforcing the Patent Local Rules.” *Finjan, Inc. v. Proofpoint, Inc.*, No. 13-CV-05808-HSG, 2015 WL 9460295, at *1 (N.D. Cal. Dec. 23, 2015). The Federal Circuit has “concluded that the exclusion of evidence is often an appropriate sanction for a party’s failure to comply with the patent local rules.” *Phigenix, Inc. v. Genentech, Inc.*, 783 F. App’x 1014, 1020 (Fed. Cir. 2019) (citing *O2 Micro Int’l Ltd. v. Monolithic Power Sys., Inc.*, 467 F.3d 1355, 1369 (Fed. Cir. 2006); *Wong v. Regents of Univ. of California*, 410 F.3d 1052, 1060 (9th Cir. 2005)).

the statements at issue from Dr. Metzker’s declaration are not material to the Court’s claim construction rulings, the Court need not rule on Spectrum’s evidentiary objections. *See Elena v. Reliance Standard Life Ins. Co.*, No. 21-CV-00390-GPC, 2022 WL 1174107, at *8 (S.D. Cal. Apr. 20, 2022) (“A court need not rule on evidentiary objections that are not material to its ruling.”); *see, e.g., Williams v. Cnty. of San Diego*, 523 F. Supp. 3d 1183, 1193–94 (S.D. Cal. 2021) (declining to rule on evidentiary objections that were not material to the district court’s ruling); *F.T.C. v. John Beck Amazing Profits, LLC*, 865 F. Supp. 2d 1052, 1062 (C.D. Cal. 2012) (“The Court need not address these objections because the Court did not rely on any portion of the evidence to which Defendants objected.”). Further, because the Court declines to rule on Spectrum’s evidentiary objections, the Court denies as moot DNA Genotek’s motion for leave to file a response to those evidentiary objections.

III. LEGAL STANDARD FOR CLAIM CONSTRUCTION

“A determination of infringement involves a two-step analysis. ‘First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process.’” *Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1320 (Fed. Cir. 2003) (quoting *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993)); *see Niazi Licensing Corp. v. St. Jude Med. S.C., Inc.*, 30 F.4th 1339, 1350 (Fed. Cir. 2022). The first step of the infringement analysis — referred to as claim construction — is now before the Court. Claim construction “is exclusively within the province of the court [to decide],” not the jury. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996); *see Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 326 (2015) (holding claim construction is an issue of law for the court to decide).

“It is a ‘bedrock principle’ of patent law that ‘the claims of a patent define the invention to which the patentee is entitled the right to exclude.’” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). “The purpose of claim

1 construction is to ‘determin[e] the meaning and scope of the patent claims asserted to be
2 infringed.’” *O2 Micro Int’l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1360 (Fed.
3 Cir. 2008).

4 Claim terms “are generally given their ordinary and customary meaning[,]” which
5 “is the meaning that the term would have to a person of ordinary skill in the art in question
6 at the time of the invention, *i.e.*, as of the effective filing date of the patent application.”
7 *Phillips*, 415 F.3d at 1312-13 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576,
8 1582 (Fed. Cir. 1996)). “In some cases, the ordinary meaning of claim language as
9 understood by a person of ordinary skill in the art may be readily apparent even to lay
10 judges, and claim construction in such cases involves little more than the application of the
11 widely accepted meaning of commonly understood words.” *Phillips*, 415 F.3d at 1314.³
12 “However, in many cases, the meaning of a claim term as understood by persons of skill
13 in the art is not readily apparent.” *O2 Micro*, 521 F.3d at 1360. If the meaning of a term is
14 not readily apparent, a court must objectively look to “those sources available to the public
15 that show what a person of skill in the art would have understood disputed claim language
16 to mean.” *Phillips*, 415 F.3d at 1314 (quoting *Innova*, 381 F.3d at 1116). “Those sources
17 include ‘the words of the claims themselves, the remainder of the specification, the
18 prosecution history, and extrinsic evidence.’” *Id.*; see *Ericsson, Inc. v. D-Link Sys., Inc.*,
19 773 F.3d 1201, 1217-18 (Fed. Cir. 2014).⁴

20 Courts first look to the language and context of the claims themselves. *See Homeland*
21 *Housewares, LLC v. Whirlpool Corp.*, 865 F.3d 1372, 1375 (Fed. Cir. 2017) (holding that
22 claim construction “begins and ends” with a claim’s actual words); *Source Vagabond Sys.*
23

24
25 ³ “General purpose dictionaries” may be instructive in determining whether the
26 ordinary meaning of claim language as understood by a person of skill in the art is readily
27 apparent. *Phillips*, 415 F.3d. at 1314.

28 ⁴ The specification is the “written description” of the invention which enables one
skilled in the art to make and use the invention and discloses the best mode of carrying out
the invention. *See* 35 U.S.C. § 112(a).

1 *Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1299 (Fed. Cir. 2014) (“a claim construction
2 analysis must begin and remain centered on the claim language itself” (quoting *Innova*,
3 381 F.3d at 1116)). Claims are interpreted subject to the standard canons of claim
4 construction. *See, e.g., id.* at 1300. For example, because a term that appears in multiple
5 claims should generally be construed consistently, “[o]ther claims of the patent in question,
6 both asserted and unasserted . . . [can] be valuable sources of enlightenment as to the
7 meaning of the [disputed] claim term.” *Phillips*, 415 F.3d at 1314 (citing *Vitronics*, 90 F.3d
8 at 1582). On the other hand, courts presume the use of different words or phrases in separate
9 claims “to indicate that the claims have different meanings and scope” under the doctrine
10 of “claim differentiation.” *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1369
11 (Fed. Cir. 2007).

12 Furthermore, “the person of ordinary skill is deemed to read the claim term not only
13 in the context of the particular claim in which the disputed term appears, but [also] in the
14 context of the entire patent, including the specification.” *Phillips*, 415 F.3d at 1314 (citing
15 *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir. 1998)). The
16 specification “is always highly relevant to the claim construction analysis. Usually it is
17 dispositive; it is the single best guide to the meaning of a disputed term.” *Vitronics*, 90 F.3d
18 at 1582; *accord Phillips*, 415 F.3d at 1317 (“It is entirely appropriate for a court, when
19 conducting claim construction, to rely heavily on the written description for guidance as to
20 the meaning of the claims.”). For example, the specification “may reveal a special
21 definition given to a claim term by the patentee that differs from the [plain and ordinary]
22 meaning it would otherwise possess. In such cases, the inventor’s lexicography governs.”
23 *Phillips*, 415 F.3d at 1316. Similarly, “[a] claim construction that excludes a preferred
24 embodiment is rarely, if ever correct and would require highly persuasive evidentiary
25 support.” *Kaufman v. Microsoft Corp.*, 34 F.4th 1360, 1372 (Fed. Cir. 2022) (quoting *Epos*
26 *Tech. Ltd. v. Pegasus Tech. Ltd.*, 766 F.3d 1338, 1347 (Fed. Cir. 2014)). As such, a court
27 must read claims “in view of the specification, of which they are a part.” *Markman v.*
28 *Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff’d*, 517 U.S. 370 (1996);

1 see 35 U.S.C. § 112(b) (“The specification shall conclude with one or more claims
2 particularly pointing out and distinctly claiming the subject matter which the inventor or a
3 joint inventor regards as the invention.”).

4 But another principle of claim construction is that “[t]he written description part of
5 the specification does not delimit the right to exclude. That is the function and purpose of
6 claims.” *Markman*, 52 F.3d at 980. As the Federal Circuit in *Phillips* explained, there is a
7 “distinction between using the specification to interpret the meaning of a claim and
8 importing limitations from the specification into the claim.” 415 F.3d at 1323. Therefore,
9 “it is improper to read limitations from a preferred embodiment described in the
10 specification—even if it is the only embodiment—into the claims absent a clear indication
11 in the intrinsic record that the patentee intended the claims to be so limited.” *Dealertrack,*
12 *Inc. v. Huber*, 674 F.3d 1315, 1327 (Fed. Cir. 2012); *accord Openwave Sys., Inc. v. Apple*
13 *Inc.*, 808 F.3d 509, 514 (Fed. Cir. 2015).

14 In addition to the claim and the specification, the patent’s prosecution history may
15 be considered if it is in evidence. *Phillips*, 415 F.3d at 1317. The prosecution history
16 “consists of the complete record of the proceedings before the PTO and includes the prior
17 art cited during the examination of the patent.” *Id.* “Like the specification, the prosecution
18 history provides evidence of how the PTO and the inventor understood the patent.” *Id.* “Yet
19 because the prosecution history represents an ongoing negotiation between the PTO and
20 the applicant, rather than the final product of that negotiation, it often lacks the clarity of
21 the specification and thus is less useful for claim construction purposes.” *Id.*

22 “In most situations, an analysis of the intrinsic evidence alone will resolve any
23 ambiguity in a disputed claim term.” *Vitronics*, 90 F.3d at 1583; *see Seabed Geosolutions*
24 *(US) Inc. v. Magseis FF LLC*, 8 F.4th 1285, 1287 (Fed. Cir. 2021) (“If the meaning of a
25 claim term is clear from the intrinsic evidence, there is no reason to resort to extrinsic
26 evidence.”). However, “[w]here the intrinsic record is ambiguous, and when necessary,”
27 district courts may “rely on extrinsic evidence, which ‘consists of all evidence external to
28 the patent and prosecution history, including expert and inventor testimony, dictionaries,

1 and learned treatises.” *Power Integrations, Inc. v. Fairchild Semiconductor Int’l, Inc.*, 711
2 F.3d 1348, 1360 (Fed. Cir. 2013) (quoting *Phillips*, 415 F.3d at 1317); *see 24/7 Customer,*
3 *Inc. v. LivePerson, Inc.*, 235 F. Supp. 3d 1102, 1107 (N.D. Cal. 2016) (“Within the class
4 of extrinsic evidence, dictionaries, and especially technical dictionaries, ‘can assist the
5 court in determining the meaning of particular terminology to those of skill in the art’
6 because they ‘endeavor to collect the accepted meanings of terms used in various fields of
7 science and technology.’” (quoting *Phillips*, 415 F.3d at 1318)).

8 While sometimes useful, “it is improper to rely on extrinsic evidence” where the
9 intrinsic evidence alone is sufficient. *Vitronics*, 90 F.3d at 1583. Indeed, a court must
10 evaluate all extrinsic evidence in light of the intrinsic evidence. *Phillips*, 415 F.3d at 1319.
11 “[E]xtrinsic evidence is to be used for the court’s understanding of the patent, not for the
12 purpose of varying or contradicting the terms of the claims.” *Genuine Enabling Tech. LLC*
13 *v. Nintendo Co.*, 29 F.4th 1365, 1373 (Fed. Cir. 2022) (quoting *Markman*, 52 F.3d at 981);
14 *see Summit 6, LLC v. Samsung Elecs. Co.*, 802 F.3d 1283, 1290 (Fed. Cir. 2015) (“Extrinsic
15 evidence may not be used ‘to contradict claim meaning that is unambiguous in light of the
16 intrinsic evidence.’” (quoting *Phillips*, 415 F.3d at 1324)). In cases where subsidiary facts
17 contained in the extrinsic evidence “are in dispute, courts will need to make subsidiary
18 factual findings about that extrinsic evidence.” *Teva*, 574 U.S. at 332.

19 Nevertheless, “district courts are not (and should not be) required to construe every
20 limitation present in a patent’s asserted claims.” *O2 Micro*, 521 F.3d at 1362. In some
21 situations, it is appropriate for a court to determine that a claim term needs no construction
22 and its plain and ordinary meaning applies. *See id.*; *Phillips*, 415 F.3d at 1314. But “[a]
23 determination that a claim term ‘needs no construction’ or has the ‘plain and ordinary
24 meaning’ may be inadequate when a term has more than one ‘ordinary’ meaning or when
25 reliance on a term’s ‘ordinary’ meaning does not resolve the parties’ dispute.” *O2 Micro*,
26 521 F.3d at 1361. When the parties present a dispute regarding the scope of a claim term,
27 it is the court’s duty to resolve the disagreement. *Id.* at 1362; *see Eon Corp. IP Holdings v.*
28 *Silver Spring Networks*, 815 F.3d 1314, 1318 (Fed. Cir. 2016).

IV. CONSTRUCTION OF THE AGREED UPON CLAIM TERMS FROM THE '187 PATENT

A. “nucleic acid”

DNA Genotek's Proposed Construction	Spectrum's Proposed Construction	Court's Construction
“a chain of nucleotides, including deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)”	“a chain of nucleotides, including deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)”	“a chain of nucleotides, including deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)”

B. “biological sample”

DNA Genotek's Proposed Construction	Spectrum's Proposed Construction	Court's Construction
“any sample containing nucleic acids that has been obtained from or deposited by an animal”	“any sample containing nucleic acids that has been obtained from or deposited by an animal”	“any sample containing nucleic acids that has been obtained from or deposited by an animal”

In their Joint Claim Construction Worksheet, the Parties agree upon the proper construction for the claim terms “nucleic acid” and “biological sample” in the '187 Patent. *See* ECF No. 74-2 at 4-5, 7. These two proposed constructions are well supported by the intrinsic record. The '187 Patent's specification sets forth express definitions for the terms “biological sample” and “nucleic acid.” *See* '187 Patent col. 7 ll. 16-19, col. 7 ll. 28-31. The Parties' joint proposed constructions for these claim terms align with those express definitions set forth in the specification. As such, the Court adopts the Parties' proposed constructions for these two claim terms. *See Phillips*, 415 F.3d at 1316 (“[T]he specification may reveal a special definition given to a claim term by the patentee In such cases, the inventor's lexicography governs.”); *Edwards Lifesciences LLC v. Cook*

Inc., 582 F.3d 1322, 1329 (Fed. Cir. 2009) (explaining that a patentee acts as his own lexicographer when the patentee “‘clearly set[s] forth a definition of the disputed claim term in either the specification or prosecution history.’”); *see, e.g., Biogen MA Inc. v. EMD Serono, Inc.*, 976 F.3d 1326, 1336 (Fed. Cir. 2020). The Court construes the claim term “nucleic acid” as “a chain of nucleotides, including deoxyribonucleic acid (DNA) or ribonucleic acid (RNA),” and the Court construes the claim term “biological sample” as “any sample containing nucleic acids that has been obtained from or deposited by an animal.”

V. CONSTRUCTION OF THE DISPUTED CLAIM TERMS FROM THE ’187 PATENT

A. “preserving/preserve”

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
The term is definite, does not require construction, and should be accorded plain and ordinary meaning. If construction is required, the term should be construed as “slowing degradation of”/“slows degradation of”	The term is indefinite.	“slowing degradation of nucleic acid[s] at room temperature for extended periods of time”/“slows degradation of nucleic acids at room temperature for extended periods of time”

Spectrum argues that the claim term “preserving/preserve” in the ’187 Patent is indefinite. ECF No. 147 at 5-10. In response, DNA Genotek contends that the term is not

indefinite and the claim term should be given its plain and ordinary meaning. ECF No. 134 at 5-12.

“Definiteness is a statutory requirement for patentability.” *Niazi*, 30 F.4th at 1346. Under 35 U.S.C. § 112 ¶ 2, a patent must “conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as the invention.” 35 U.S.C. § 112 ¶ 2 (pre-AIA).⁵

“A claim fails to satisfy this statutory requirement and is thus invalid for indefiniteness if its language, when read in light of the specification and the prosecution history, ‘fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention.’” *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1369–70 (Fed. Cir. 2014) (quoting *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014)). This “reasonable certainty” standard “reflects a ‘delicate balance’ between ‘the inherent limitations of language’ and providing ‘clear notice of what is claimed.’” *Guangdong Alison Hi-Tech Co. v. Int’l Trade Comm’n*, 936 F.3d 1353, 1359 (Fed. Cir. 2019). “Th[e] standard ‘mandates clarity, while recognizing that absolute precision is unattainable.’” *Nevro Corp. v. Bos. Sci. Corp.*, 955 F.3d 35, 39 (Fed. Cir. 2020) (quoting *Nautilus*, 572 U.S. at 910); *see also BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017) (“‘Reasonable certainty’ does not require ‘absolute or mathematical precision.’”).

“General principles of claim construction apply to indefiniteness allegations.” *HZNP Medicines LLC v. Actavis Lab’ys UT, Inc.*, 940 F.3d 680, 688 (Fed. Cir. 2019). The party asserting indefiniteness bears “the burden of proving indefiniteness by clear and convincing evidence.” *BASF*, 875 F.3d at 1365 (citing *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1377 (Fed. Cir. 2015)); *see also Microsoft Corp. v. i4i Ltd. P’ship*,

⁵ “Congress amended § 112 when it enacted the Leahy–Smith America Invents Act (‘AIA’).” *In re Durance*, 891 F.3d 991, 1002 n.9 (Fed. Cir. 2018). “However, the amended version of § 112 applies only to patent applications ‘filed on or after’ September 16, 2012.” *Id.* Here, the Parties agree that the pre-AIA version of § 112 applies to the ’187 Patent. *See, e.g.*, ECF No. 147 at 5; ECF No. 134 at 19.

564 U.S. 91, 95 (2011) (holding that 35 U.S.C. § 282 “requires an invalidity defense to be proved by clear and convincing evidence”).

The Court begins its analysis of this issue by noting that both the claim language and the specification of the ’187 Patent provide clear guidance on how to achieve the claimed “preserving” of nucleic acids. Independent claim 1 of the ’187 Patent recites a device “for . . . **preserving nucleic acid** in a biological sample” comprising, among other things:

reagents in the reagent compartment for **preserving nucleic acids** potentially present in the sample wherein said reagents comprise a denaturing agent, a chelator and a buffer agent; and,

. . . release said reagents to form a mixture of reagents and said biological sample wherein said buffering agent maintains a pH of said mixture equal to or above 5.0 to **preserve nucleic acids** potentially present in the sample.

’187 Patent col. 19 ll. 34-35, 49-52, 56-59 (emphasis added); *see also id.* col. 3 ll. 61-64 (“[A] first aspect of the invention features a composition for preserving nucleic acids that includes a chelating agent, and a denaturing agent, where the pH of the composition is greater than 5.0.”). Here, the claim language and the specification provide clear guidance to a PHOSITA as to the specific reagents to include in the device for achieving the claimed “preserving” of nucleic acids potentially present in the biological sample. *See* ECF No. 134-1, Metzker Decl. ¶¶ 54-57; ECF No. 134-6, Ex. 1 at 30-35, 39, 40-41, 45-46; *see also BASF*, 875 F.3d at 1368 (rejecting indefiniteness challenge in part because “[b]oth parties’ experts agreed that materials capable of performing the claimed reactions were known in the art at the time of the invention”). Indeed, Spectrum itself asserts: “The [’187] patent includes substantial detail about the reagents that make up the composition of the invention. The patent also demonstrates, with examples, how the composition preserves the nucleic acids for extended periods of time.” ECF No. 147 at 2 (citations omitted).

Despite this guidance, Spectrum argues that the claim term “preserving/preserve” is indefinite because the claim language does not specify a time period (*i.e.*, how long the nucleic acid must be maintained to be considered preserved), and the claim language does

1 not specify the temperature at which the sample is stored. ECF No. 147 at 5, 7 (citing ECF
2 No. 87, Fischetti Decl. ¶¶ 23, 35-37); *see* ECF No. 88 at 4. But in evaluating indefiniteness,
3 the Court is not limited to only the claim language. Rather, “in assessing indefiniteness,”
4 the Court must evaluate the claim language “in light of the specification and the
5 prosecution history.” *Nautilus*, 572 U.S. at 908; *accord Interval Licensing*, 766 F.3d at
6 1371.

7 The specification of the ’187 Patent provides guidance to a PHOSITA as to both
8 time period and temperature. The specification states: “The present invention relates to
9 compositions and methods for preserving nucleic acids at room temperature for extended
10 periods of time” ’187 Patent col. 1 ll. 23-25. The specification further states: “The
11 present inventor has developed a composition, which, when mixed with a mucin-containing
12 bodily fluid, preserves the nucleic acids at room temperature under ambient conditions for
13 extended periods of time.” *Id.* col. 3 ll. 48-51; *see also id.* col. 13 ll. 44-47 (“Incubation
14 can be at room temperature over a relatively long period of time (days or weeks) while
15 samples are being shipped to a laboratory for analysis.”), col. 16 ll. 19-20 (“The container
16 can be mailed back to the testing lab at room temperature.”), col. 16 ll. 54-55 (“stabilizes
17 DNA for longer periods of time”). In these passages, the specification clearly states that
18 within the meaning of the ’187 Patent, the nucleic acids are able to be preserved at room
19 temperature and for extended periods of time. As such, contrary to Spectrum’s assertions,
20 the ’187 Patent’s specification gives guidance to a PHOSITA as to both the time period
21 and the temperature for the claimed “preserving.”

22 Spectrum’s expert Dr. Fischetti acknowledges these passages in the specification,
23 but contends that they are insufficient because they do not provide a specific time period
24 or a specific temperature for the nucleic acid preservation. ECF No. 87, Fischetti Decl. ¶¶
25 33, 37. The Court rejects this contention. “[A] claim is not indefinite just because it is
26 broad.” *Niazi*, 30 F.4th at 1347; *see BASF*, 875 F.3d at 1367 (“[B]readth is not
27 indefiniteness.”). Thus, “a patentee need not define his invention with mathematical
28 precision in order to comply with the definiteness requirement.” *Guangdong Alison*, 936

F.3d at 1359 (quoting *Sonix Tech. Co. v. Publications Int’l, Ltd.*, 844 F.3d 1370, 1377 (Fed. Cir. 2017)); see *One-E-Way, Inc. v. Int’l Trade Comm’n*, 859 F.3d 1059, 1066 (Fed. Cir. 2017) (holding “[f]or purposes of definiteness, the term is not required to have a technical measure”). “Indeed, patentees often use descriptive words to avoid a strict numerical boundary to the specified parameter.” *Niazi*, 30 F.4th at 1347 (cleaned up); see *Guangdong Alison*, 936 F.3d at 1360. As such, the patentee is free to use broad words to describe the time period and the temperature for the claimed nucleic acid preservation. The patentee did not need to identify specific numerical boundaries as to the time period (*i.e.*, a specific amount of days or weeks) or the temperature (*i.e.*, a specific temperature range) in order to comply with § 112’s definiteness requirement.⁶

Spectrum also argues that the claim term “preserving/preserve” is indefinite because the claims do not specify the type of assay that should be used to determine if the nucleic acid has been preserved. ECF No. 147 at 7 (citing ECF No. 87, Fischetti Decl. ¶¶ 21-22). Again, the specification provides guidance to a PHOSITA on this issue. Spectrum’s expert Dr. Fischetti acknowledges that the specification expressly references both electrophoresis and polymerase chain reaction (“PCR”), and those are both well-known detection techniques for examining the presence or absence of a target nucleotide sequence in a sample. See ECF No. 87, Fischetti Decl. ¶ 21 (citing ’187 Patent col. 16 ll. 56 to col. 18 ll. 8). As such, the ’187 Patent’s specification gives guidance to a PHOSITA as to detection methods that may be used to determine if nucleic acids in the sample have been preserved.

Spectrum also argues that “[t]he term ‘preserving nucleic acids’ does not have a

⁶ The Court notes that in its briefing, Spectrum shows that it understands the meaning of the term “room temperature,” defining it as “(20-25 °C).” ECF No. 147 at 7. In addition, the Court notes that the specification provides additional guidance as to what is meant by the phrase “extended period of time.” Elsewhere, the specification states: “Incubation can be at room temperature over a relatively long period of time (days or weeks) while samples are being shipped to a laboratory for analysis.” ’187 Patent col. 13 ll. 44-47. Here, the specification clarifies that when referring to extended periods of time, the specification is referring to days or weeks.

1 single meaning to those in the relevant field.” ECF No. 147 at 6 (citing ECF No. 87,
2 Fischetti Decl. ¶ 18 (“[I]n 2002, the term ‘preserving nucleic acid’ did not have just one
3 meaning in the biological sciences.”)). But even assuming this is true, this is insufficient to
4 prove indefiniteness of a patent claim. Under the standard for evaluating indefiniteness set
5 forth by the Supreme Court in *Nautilus*, the Court does not ask whether a PHOSITA
6 examining the claim term by itself in the abstract would possess reasonable certainty as to
7 the scope of the term. Rather, the Court must inquire whether a PHOSITA examining the
8 claim term along with the other claim language, the specification, and the prosecution
9 history, would possess reasonable certainty as to the scope of the claim. *See Nautilus*, 572
10 U.S. at 901, 908 (“[I]n assessing definiteness, claims are to be read in light of the patent’s
11 specification and prosecution history.”); *Interval Licensing*, 766 F.3d at 1371. As explained
12 above, the specification along with the claim language gives clear guidance to a PHOSITA
13 as to the meaning of the claim term “preserving nucleic acids” within the scope of the ’187
14 Patent. Moreover, the Court notes that the extrinsic evidence cited by Dr. Fischetti to
15 support his factual assertion that there is not a single meaning for the term “preserving
16 nucleic acid” itself sets forth a common meaning for the term. The cited article states:
17 “[T]he term ‘preservation’ is used by all these fields and refers to the maintenance of
18 chemical and physical integrity of the DNA molecule.” ECF No. 87, Fischetti Decl. ¶ 18.
19 As such, the cited evidence contradicts Dr. Fischetti’s assertion that there is no common
20 meaning for that term.

21 In addition, that the claim term “preserving/preserve” is definite is supported by
22 evidence that Spectrum presented during IPR proceedings before the PTAB. The Federal
23 Circuit has explained that application of the term at issue by a challenger’s own expert to
24 various references and products without any uncertainty “supports the conclusion that a
25 skilled artisan did understand the term with reasonable certainty.” *Sonix*, 844 F.3d at 1380;
26 *see also Liqwd, Inc. v. L’Oreal USA, Inc.*, 720 F. App’x 623, 631 (Fed. Cir. 2018)
27 (“Evidence of a challenger’s own ability to apply a term without unreasonable uncertainty
28 counts against an indefiniteness contention.”). In IPR proceedings as to a different patent,

U.S. Patent No. 10,767,215 (“the ’215 Patent”), Spectrum submitted a declaration from its expert, Dr. Fischetti, the same expert in this action. *See* ECF No. 134-10, Ex. 5 ¶¶ 53-115. In the declaration, Dr. Fischetti performs an invalidity analysis, opining that the prior art references Birnboim (the invention disclosed in the ’187 Patent) and Stefan render certain claims from the ’215 Patent obvious under 35 U.S.C. § 103. *See id.* ¶¶ 53-115. In that analysis, Dr. Fischetti is able to apply the term “preserving” from the invention disclosed in the ’187 Patent to the relevant elements in the ’215 Patent without any uncertainty. *See id.* ¶¶ 63, 68-70, 75, 79-81; *see also* ECF No. 134-9, Ex. 4 ¶¶ 65, 73, 107 (Spectrum’s expert Dr. Taylor describing and applying the claim term “preserving” to the patent at issue in the IPR without any uncertainty). This supports the conclusion that a skilled artisan did and would understand the claim term “preserving/preserve” with reasonable certainty. *See Sonix*, 844 F.3d at 1380; *see, e.g., Taction Tech., Inc. v. Apple Inc.*, No. 3:21-cv-812-TWR-JLB, ECF No. 141 at 20-22 (S.D. Cal. Sept. 28, 2022) (relying on accused infringer and its expert’s ability to apply claim term without issue during their invalidity analysis in IPR proceedings in rejecting indefiniteness challenge). In sum, Spectrum has failed to demonstrate that the claim term “preserving/preserve” is indefinite.⁷

Turning to construction of the claim term “preserving/preserve,” DNA Genotek

⁷ At the claim construction hearing, Spectrum noted that if the Court rejects its indefiniteness challenge at claim construction, it is not “a dispositive judgment” on its indefiniteness counterclaim and defense in this case, and it is still preserved as an invalidity defense for trial. ECF No. 176 at 4. The Court acknowledges that in rejecting Spectrum’s indefiniteness challenge in this claim construction order, the Court is not entering a judgment against Spectrum on its indefiniteness counterclaim or defense. But, as DNA Genotek correctly noted, indefiniteness is an issue of law for the Court to decide. *See Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341, 1342 (Fed. Cir. 2015) (“The internal coherence and context assessment of the patent, and whether it conveys claim meaning with reasonable certainty, are questions of law.”); *Nature Simulation Sys. Inc. v. Autodesk, Inc.*, 50 F.4th 1358, 1360 (Fed. Cir. 2022) (“Claim indefiniteness is a legal conclusion.”). And the Court has provided a thorough analysis as to the merits of Spectrum’s theory of indefiniteness above.

1 argues that if the claim term must be construed, then it should be construed as “slowing
2 degradation of”/“slows degradation of.” ECF No. 134 at 5. The Court notes that during his
3 deposition, Spectrum’s expert, Dr. Fischetti, described “preservation” as “using a
4 combination of compounds to help slow down the degradation process.” ECF No. 134-6 at
5 46. As such, the Court will include “slowing degradation of” in its construction for this
6 claim term.

7 Moreover, as previously noted, the specification contains a clear disclaimer
8 explaining that “[t]he present invention relates to compositions and methods for preserving
9 nucleic acids at room temperature for extended periods of time” ’187 Patent col. 1 ll.
10 23-25. “When a patentee ‘describes the features of the ‘present invention’ as a whole,’ he
11 implicitly alerts the reader that ‘this description limits the scope of the invention.’”
12 *Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1353 (Fed. Cir. 2016)
13 (quoting *Regents of Univ. of Minnesota v. AGA Med. Corp.*, 717 F.3d 929, 936 (Fed. Cir.
14 2013)); accord *Pacing Techs., LLC v. Garmin Int’l, Inc.*, 778 F.3d 1021, 1025 (Fed. Cir.
15 2015); see, e.g., *Wastow Enterprises, LLC v. Truckmovers.com, Inc.*, 855 F. App’x 748,
16 750–51 (Fed. Cir. 2021); *Honeywell Int’l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1318
17 (Fed. Cir. 2006); see also *Poly-Am., L.P. v. API Indus., Inc.*, 839 F.3d 1131, 1136 (Fed.
18 Cir. 2016) (“[A]n inventor may disavow claims lacking a particular feature when the
19 specification describes “the present invention” as having that feature.”). As such, the Court
20 will also include this disclaimer in its construction for this claim term. Accordingly, the
21 Court construes “preserving nucleic acid[s]” as “slowing degradation of nucleic acid[s] at
22 room temperature for extended periods of time,” and the Court construes “preserves nucleic
23 acids” as “slows degradation of nucleic acids at room temperature for extended periods of
24 time.”

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B. “containment vessel”

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
No construction required, plain and ordinary meaning	“container”	“container”

Here, the Parties dispute whether the claimed “containment vessel” must be a “container” or something broader. Spectrum contends that the “containment vessel” claimed in the ’187 Patent is simply a container. ECF No. 147 at 10. In response, DNA Genotek argues that the meaning of “containment vessel” would be readily apparent to the Court and a jury by its plain and ordinary meaning, and Spectrum has failed to give a reason for deviating from that plain and ordinary meaning. ECF No. 134 at 15.

The Court begins its analysis of the Parties’ dispute by reviewing the claim language. Independent Claim 1 of the ’187 Patent recites a device comprising, among other things:

- a. one or more walls defining a **containment vessel** having a top having an opening, and a closed bottom having a sample receiving area for holding said biological sample, said opening for receiving a liquid sample and for sealably receiving a sealing cap, said top having an opening for receiving a biological sample from the mouth of a user and further comprising at least one marking on said one or more walls which corresponds to a fluid volume in the sample receiving area;

’187 Patent col. 19 ll. 34-44 (emphasis added). Here, the claim language describes the “containment vessel” as a container. First, the claim language uses the word “vessel.” The common meaning of the word “vessel” in this context is a container for holding something. *See* MERRIAM-WEBSTER DICTIONARY, <https://www.merriam-webster.com/dictionary/vessel> (defining “vessel” as “a container (such as a cask, bottle, kettle, cup, or bowl) for holding something”); CAMBRIDGE DICTIONARY, <https://dictionary.cambridge.org/>

1 dictionary/english/vessel (defining “vessel” as “a curved container that is used to hold
2 liquid”); *see also Phillips*, 415 F.3d at 1314 (explaining that the use of general purpose
3 dictionaries “may be helpful” in cases that involve “little more than the application of the
4 widely accepted meaning of commonly understood words”). That meaning is consistent
5 with the claim language as claim 1 explains that the “containment vessel” has walls and a
6 closed bottom for holding the biological sample. *See* ’187 Patent col. 18 ll. 36-39. As such,
7 the claim language supports Spectrum’s proposed construction.

8 The specification further supports Spectrum’s proposed construction. Although the
9 specification never uses the specific term “containment vessel,” when the specification
10 describes the component of the claimed invention that holds the biological sample, it refers
11 to that component as a “container.” *See, e.g.,* ’187 Patent col. 6 ll. 8-9 (“placing the bodily
12 fluid into a first region of a container”), col. 6 ll. 28-29 (“The device includes: a container
13 that has a first region for collecting a biological sample”), col. 14 ll. 51-52. As such,
14 Spectrum’s proposed construction is well supported by the intrinsic record.

15 DNA Genotek argues that Spectrum’s proposed construction is improper because
16 the Court should not give a claim term a narrower construction unless it is prescribed by
17 the specification or the prosecution history. ECF No. 134 at 15; ECF No. 89 at 6. DNA
18 Genotek argues that “[a] ‘patentee is free to choose a broad term and expect to obtain the
19 full scope of its plain and ordinary meaning unless the patentee explicitly redefines the
20 term or disavows its full scope.’” ECF No. 89 at 6 (quoting *Thorner v. Sony Computer Ent.*
21 *Am. LLC*, 669 F.3d 1362, 1367 (Fed. Cir. 2012)). But DNA Genotek fails to articulate
22 precisely how Spectrum’s proposed construction purportedly narrows the scope of the
23 claim term “containment vessel.” And DNA Genotek fails to articulate what it precisely
24 considers to be the proper scope of the claim term “containment vessel.” DNA Genotek
25 itself contends that the meaning of the term “containment vessel” would be readily apparent
26 to the Court and the jury by its plain and ordinary meaning. ECF No. 134 at 15; *see* ECF
27 No. 89 at 6. The readily apparent plain meaning of the word “vessel” is a “container” for
28 holding something. *See* MERRIAM-WEBSTER DICTIONARY, <https://www.merriam->

webster.com/dictionary/vessel; CAMBRIDGE DICTIONARY, <https://dictionary.cambridge.org/dictionary/english/vessel>.

At the claim construction hearing, DNA Genotek argued that rephrasing the plain language of a claim by substituting synonyms is not the purpose of claim construction. ECF No. 176 at 13 (citing *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 863 (Fed. Cir. 2004)). The Court acknowledges that in *C.R. Bard*, the Federal Circuit explained that courts should forgo detailed dictionary analysis during claim construction if the term is commonplace, and “‘merely rephrasing or paraphrasing the plain language of a claim by substituting synonyms does not represent genuine claim construction.’” 388 F.3d at 863; *see also U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) (Claim construction “is not an obligatory exercise in redundancy.”); *O2 Micro*, 521 F.3d at 1362 (“[D]istrict courts are not (and should not be) required to construe every limitation present in a patent’s asserted claims.”). But the Federal Circuit has also explained in *O2 Micro* and *Eon*, that if the parties present a dispute regarding the scope of a claim term, it is the court’s duty to resolve the dispute. *O2 Micro*, 521 F.3d at 1362; *see Eon*, 815 F.3d at 1318. Although the parties appear to agree that “container” is a synonym for “vessel,” [see ECF No. 176 at 13-14], the parties are unable to represent to the Court that they are in agreement as to the scope of this claim term. As such, the Court construes this claim term in order to resolve the parties’ dispute.

In sum, the Court adopts Spectrum’s proposed construction. The Court construes the term “containment vessel” as “container.”

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C. **“said opening for receiving a liquid sample[,] for sealably receiving a sealing cap, [and] for receiving a biological sample from the mouth of the user”**

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
The term does not require construction and should be accorded plain and ordinary meaning.	“said opening configured to be closed with a sealing cap to prevent leakage and having a diameter of at least 2.0 cm so that it can receive a liquid [biological sample] directly from the mouth of the user”	“the opening is able to receive a liquid biological sample directly from the mouth of the user”

Here, the Parties’ dispute regarding this claim term is two-part. First, the Parties dispute whether the claimed “opening” is specifically configured for receiving a liquid biological sample directly from the mouth of a user. ECF No. 147 at 11-12. Second, the Parties dispute whether the claimed “opening” must have a diameter of at least 2.0 cm. ECF No. 147 at 13-14. The Court addresses each of these disputes below.

The Court first addresses Spectrum’s contention that the opening be configured so that it can receive a liquid sample directly from the mouth of the user. Beginning with the claim language, independent claim 1 of the ’187 Patent recites a device comprising, among other things:

- a. one or more walls defining a containment vessel having a top having an opening, . . . **said opening for receiving a liquid sample and for sealably receiving a sealing cap, said top having an opening for receiving a biological sample from the mouth of a user. . . ;**

1 '187 Patent col. 19 ll. 36-42 (emphasis added). Here, the claim language provides support
2 for Spectrum's proposed construction. The claim language explains that the containment
3 vessel has an opening, and one of the purposes of that opening is for receiving a liquid
4 biological sample from the mouth of a user. *Id.* at col. 19 ll. 36-42. That the claim language
5 uses the phrase "from the mouth of a user" implies that the liquid sample is sent from the
6 mouth of the user into the opening. As such, the claim language is consistent with this
7 portion of Spectrum's proposed construction.

8 Spectrum argues that its proposed construction is additionally supported by a
9 disclaimer in the prosecution history. ECF No. 147 at 11-12. "Prosecution disclaimer
10 'preclud[es] patentees from recapturing through claim interpretation specific meanings
11 disclaimed during prosecution.'" *Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1359
12 (Fed. Cir. 2017) (quoting *Omega*, 334 F.3d at 1323). "[T]he doctrine of prosecution
13 disclaimer ensures that claims are not 'construed one way in order to obtain their allowance
14 and in a different way against accused infringers.'" *Id.* at 1360 (quoting *Southwall Techs.,*
15 *Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995)).

16 "Such disclaimer can occur through amendment or argument." *Id.* at 1359. But "[f]or
17 a statement during prosecution to qualify as a disavowal of claim scope, it must be 'so clear
18 as to show reasonable clarity and deliberateness,' and 'so unmistakable as to be
19 unambiguous evidence of disclaimer.'" *Genuine Enabling Tech. LLC v. Nintendo Co.*, 29
20 F.4th 1365, 1374 (Fed. Cir. 2022); *see also Aylus*, 856 F.3d at 1361 ("[T]o invoke the
21 doctrine of prosecution disclaimer, any such statements must 'be both clear and
22 unmistakable.'"); *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed.
23 Cir. 2008) ("Prosecution disclaimer does not apply to an ambiguous disavowal."). "Thus,
24 when the patentee unequivocally and unambiguously disavows a certain meaning to obtain
25 a patent, the doctrine of prosecution history disclaimer narrows the meaning of the claim
26 consistent with the scope of the claim surrendered." *Biogen Idec, Inc. v. GlaxoSmithKline*
27 *LLC*, 713 F.3d 1090, 1095 (Fed. Cir. 2013). "A patentee could do so, for example, by
28 clearly characterizing the invention in a way to try to overcome rejections based on prior

art.” *Computer Docking Station*, 519 F.3d at 1374. “The party seeking to invoke prosecution history disclaimer bears the burden of proving the existence of a clear and unmistakable disclaimer that would have been evident to one skilled in the art.” *Genuine Enabling Tech.*, 29 F.4th at 1374.

Here, Spectrum specifically relies on statements from the prosecution of U.S. Patent No. 9,523,115 (“the ’115 Patent”) to support its claim of prosecution history disclaimer. See ECF No. 147 at 12. The ’187 Patent is a continuation of the ’115 Patent. ’187 Patent at [63]. “[P]rosecution disclaimer may arise from disavowals made during the prosecution of ancestor patent applications.” *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007) (quoting *Omega*, 334 F.3d at 1333). “When the application of prosecution disclaimer involves statements from prosecution of a familial patent relating to the same subject matter as the claim language at issue in the patent being construed, those statements in the familial application are relevant in construing the claims at issue.” *Id.*; see *E.I. du Pont De Nemours & Co. v. Unifrax I LLC*, 921 F.3d 1060, 1070 (Fed. Cir. 2019) (“When a parent application includes statements involving ‘common subject matter’ with the terms at issue, those statements are relevant to construction of the terms in the child patent.”).

During prosecution of the ’115 Patent, the examiner rejected certain claims as obvious under 35 U.S.C. § 103 in light of three prior art references: Baker, Lawrence, and Verscheure. ECF No. 83-5, Ex. 4 at 229-33. In response to these rejections, the patentee amended its claims, including Claim 30,⁸ and argued:

Reconsideration of the present rejection is respectfully requested.

⁸ Claim 30 as amended included the following claim language: “said top having an opening for receiving a biological sample from the mouth of a user.” ECF No. 83-5 at 215 (emphasis in original). This language is identical to the language contained in independent claim 1 of the ’187 Patent. Compare *id.* with ’187 Patent col. 19 ll. 40-42; see also *Regents of Univ. of Minnesota v. AGA Med. Corp.*, 717 F.3d 929, 943 (Fed. Cir. 2013) (“In general, a prosecution disclaimer will only apply to a subsequent patent if that patent contains the same claim limitation as its predecessor.”).

Applicant respectfully submits the present rejections totally fail to address key features recited in independent claim 30. The rejections fail to address the **opening for receiving a sample directly from the mouth** and having indicia on the one or more walls that correspond to the desired fluid level of the sample.

...

The device disclosed by Lawrence is not well adapted to receive [a] sample **directly from the mouth**. . . . The samples [disclosed by Lawrence] are not taken **directly from the mouth**. . . . Although sputum is casually mentioned as a sample it is not clear that the sputum would be delivered **directly to the device** which is also engineered to receive an insect, small animal, fungus, plant or animal tissue.

Id. at 221 (emphasis added). Here, the patentee expressly distinguished the claimed invention from the Lawrence reference on the grounds that Lawrence purportedly did not have an opening for receiving a sample “directly” from the mouth. *Id.* Indeed, subsequently, the examiner acknowledged that in making these arguments, the patentee appeared to be construing the relevant claim term “to mean that the sample is directly transferred from the mouth to the opening (*i.e.*, spitting into the opening).” *Id.* at 195.

The patentee further confirmed this understanding of the scope of the term “opening” during the prosecution history. The examiner also rejected certain claim terms as obvious in light of the prior art references: Baker, Lawrence, Verscheure, and Shuber. *Id.* at 200-01; *see also id.* at 233. In response to these additional rejections, the patentee argued: “Applicant respectfully submits Shuber does not address the specialized purpose of the present invention to receive samples directly from the mouth, and therefore fails to remedy the deficiencies of Baker, Lawrence and Verscheure.” *Id.* at 164; *accord id.* at 223. The Court agrees with Spectrum that these statements in the prosecution history constitute clear and unmistakable disavowals requiring that the claimed “opening” be for receiving liquid samples “directly” from the mouth of the user. *See Computer Docking Station*, 519 F.3d at

1 1374 (“A patentee could [make a disclaimer], for example, by clearly characterizing the
2 invention in a way to try to overcome rejections based on prior art”); *Purdue Pharma L.P.*
3 *v. Endo Pharms. Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006) (Prosecution disclaimer “may
4 occur, for example, when the patentee explicitly characterizes an aspect of his invention in
5 a specific manner to overcome prior art.”); *MBO Lab’ys, Inc. v. Becton, Dickinson & Co.*,
6 474 F.3d 1323, 1330 (Fed. Cir. 2007) (“Prosecution arguments like this one which draw
7 distinctions between the patented invention and the prior art are useful for determining
8 whether the patentee intended to surrender territory, since they indicate in the inventor’s
9 own words what the invention is not.”).⁹

10 In sum, Spectrum’s contention that the claimed “opening” must be configured to
11 receive a liquid biological sample directly from the mouth of the user is well supported by
12 the intrinsic record, specifically the disclaimers contained in the prosecution history. As
13 such, the Court will include the requirement that the claimed “opening” be for receiving a
14 liquid biological sample directly from the mouth of a user in its construction for this claim
15 term.

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19 ⁹ At the claim construction hearing, DNA Genotek contended that in the prosecution
20 history at issue, the examiner did not accept its arguments regarding the scope of the
21 relevant claim term. ECF No. 176 at 54. In response, Spectrum correctly explained that
22 this is of no consequence because when a patentee makes a disclaimer in the prosecution
23 history, that particular characterization of the claimed invention need not be accepted by
24 the examiner in order for prosecution history disclaimer to apply. *Id.* at 55. The Federal
25 Circuit holds “patentees to distinguishing statements made during prosecution even if they
26 said more than needed to overcome a prior art rejection.” *Data Engine Techs. LLC v.*
27 *Google LLC*, 10 F.4th 1375, 1383 (Fed. Cir. 2021); *see, e.g., Tech. Props. Ltd. LLC v.*
28 *Huawei Techs. Co.*, 849 F.3d 1349, 1358 (Fed. Cir. 2017) (“The patentee’s disclaimer may
not have been necessary, but its statements made to overcome Magar were clear and
unmistakable.”); *CliniComp Int’l, Inc. v. Cerner Corp.*, No. 17CV02479GPCDEB, 2022
WL 3006343, at *8 (S.D. Cal. July 28, 2022) (“Those statements regarding partitioning
might not have been necessary to distinguish the claimed invention from the prior art.
Nevertheless, they were clear and unmistakable and constitute prosecution disclaimers.”).

1 Turning to the second part of the Parties' dispute, the Court notes that there is
2 nothing in the claim language requiring that the opening be at least 2.0 cm in diameter. *See*
3 '187 Patent col. 19 ll. 34-44. Indeed, the claim language says nothing at all about the
4 diameter of the opening. *See id.* As such, the claim language does not support Spectrum's
5 contention that the claimed "opening" must be at least 2.0 cm in diameter.

6 Spectrum argues that the specification supports the notion that the "opening" must
7 be at least 2.0 cm. ECF No. 147 at 13. But to support this argument, Spectrum first relies
8 on a passage from the specification explaining that "[t]he collection device of the
9 invention" has "a broad mouth." *See* '187 Patent col. 14 ll. 61, col. 15 ll. 1. The Court
10 acknowledges that, here, the specification is discussing the claimed invention as a whole
11 and not merely a preferred embodiment. *See id.* But a statement that the claimed "opening"
12 has a broad mouth says nothing about the specific diameter of said opening. As such, this
13 is insufficient to support Spectrum's proposed construction.

14 Second, Spectrum relies on the following passage from the specification: "The first
15 region can have an opening of from 2.0 to 7.0 cm, desirably from 2.5 to 3.5 cm, and most
16 desirably 3.0 cm." '187 Patent col. 6 ll. 36-39. But "[a]bsent a clear disavowal or contrary
17 definition in the specification or the prosecution history, the patentee is entitled to the full
18 scope of its claim language." *Aug. Tech. Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1286 (Fed.
19 Cir. 2011); *see Thorner*, 669 F.3d at 1366. Here, there is no clear disavowal. To the
20 contrary, in the passage at issue, the specification uses permissive language in stating that
21 the first region "can" have an opening of those diameters. '187 Patent col. 6 ll. 37. The
22 specification does not require those diameters. In sum, the specification does not support
23 Spectrum's contention that the claimed "opening" must be at least 2.0 cm in diameter.

24 To support its contention, Spectrum also cites to the prosecution history, specifically
25 statements from U.S. Provisional Patent Application 60/386,398 ("the '398 Provisional").
26 ECF No. 147 at 13. Specifically, Spectrum cites to a passage from the '398 Provisional
27 stating that the sample collection tube "has a wide mouth, approx. 2.5 to 4 cm in diameter
28 to make it easier to spit saliva into it." ECF No. 83-7, Ex. 6 at 216 ll. 17-20. However, the

1 cited passage is in a section called “EXAMPLES” and immediately preceding this section,
2 the ’398 Provisional states: “The following examples are illustrative but not intended to be
3 limiting of the embodiment of the invention.” *Id.* at 261 ll. 1-4. As such, the cited language
4 is insufficient to constitute a disclaimer of claim scope, and the prosecution history does
5 not support Spectrum’s contention. *See Aylus*, 856 F.3d at 1361 (explaining that a
6 disclaimer must “‘be both clear and unmistakable’”).

7 Finally, Spectrum cites to extrinsic evidence, specifically DNA Genotek internal
8 documents. ECF No. 147 at 13-14 (citing ECF No. 147, Ex. 18). This extrinsic evidence is
9 not persuasive. “If the meaning of a claim term is clear from the intrinsic evidence, there
10 is no reason to resort to extrinsic evidence.” *Seabed Geosolutions*, 8 F.4th at 1287; *see also*
11 *Summit 6*, 802 F.3d at 1290 (“Extrinsic evidence may not be used ‘to contradict claim
12 meaning that is unambiguous in light of the intrinsic evidence.’”). Further, “it is improper
13 to import a limitation into a claim where the limitation has no basis in the intrinsic record.”
14 *Seachange Int’l, Inc. v. C-COR, Inc.*, 413 F.3d 1361, 1376 (Fed. Cir. 2005). As explained
15 above, a review of the intrinsic record does not support the inclusion of the limitation
16 proposed by Spectrum that the opening be at least 2.0 cm in diameter. As such, Spectrum
17 cannot rely on extrinsic evidence alone to support the inclusion of that limitation.¹⁰ *See*
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21 ¹⁰ Moreover, even if the Court were to consider the contents of the extrinsic evidence
22 at issue, it still is not persuasive. Nothing in the documents identify the documents as
23 specifically discussing the technology claimed in the ’187 Patent. *See* ECF No. 147, Ex.
24 18. The documents appear to be at most discussing potential commercial embodiments.
25 *See id.*

26 “Just as claims should not be limited to preferred embodiments described in the
27 specification, claims should not be limited to commercial embodiments.” *Taction*, No.
28 3:21-cv-812-TWR-JLB, ECF No. 141 at 16 n.7 (citing *Int’l Visual Corp. v. Crown Metal*
Mfg. Co., 991 F.2d 768, 77172 (Fed. Cir. 1993) (finding district court erred by relying on
the patentee’s commercial embodiment to limit the scope of the claims during claim
construction)). “[C]laim construction . . . focuses on the recited limitations of the claims,
not on the features of a commercial embodiment of the invention.” *Myco Indus., Inc. v.*

Seabed Geosolutions, 8 F.4th at 1287; *Seachange Int'l*, 413 F.3d at 1376.

In sum, the Court adopts in part Spectrum's proposed construction. The Court construes the term "an opening for receiving a biological sample from the mouth of the user"¹¹ as "the opening is able to receive a liquid biological sample directly from the mouth of the user."

D. "reagent compartment"

DNA Genotek's Proposed Construction	Spectrum's Proposed Construction	Court's Construction
The term does not require construction and should be accorded plain and ordinary meaning.	"region or section of the [containment vessel]"	"region or section of the containment vessel"

Here, the Parties dispute whether the claimed "reagent compartment" in the '187 Patent must specifically be a region or section of the containment vessel. Spectrum asserts

BlephEx, LLC, 955 F.3d 1, 15 (Fed. Cir. 2020). As such, Spectrum's extrinsic evidence is irrelevant for claim construction purposes.

¹¹ In its claim construction brief, Spectrum specifically requests that the Court construe the claim term "said opening for receiving a liquid sample[,] for sealably receiving a sealing cap, [and] for receiving a biological sample from the mouth of the user." See ECF No. 147 at 11. In adopting in part Spectrum's proposed construction, the Court agrees with Spectrum that the prosecution history contains a disclaimer requiring that the sample is received directly from the mouth of the user. But in order to implement that disclaimer, the Court need only construe the specific claim term "an opening for receiving a biological sample from the mouth of the user" rather than the broader claim term proposed by Spectrum. Spectrum has not provided the Court with a sufficient basis for deviating from the plain and ordinary meaning as to the remainder of the claim language Spectrum identifies. *Cf. Eon*, 815 F.3d at 1318 ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy." (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))); *U.S. Surgical*, 103 F.3d at 1568 (claim construction "is not an obligatory exercise in redundancy").

1 that the “reagent compartment” must be in the containment vessel because DNA Genotek
2 has expressly disavowed any claim scope that would cover devices with a reagent
3 compartment located in the cap. ECF No. 147 at 14. DNA Genotek argues that the term
4 “reagent compartment” should be given its plain and ordinary meaning, and the claims and
5 the specification of the ’187 Patent do not require that the reagent compartment be located
6 within the containment vessel – as opposed to the cap or elsewhere. ECF No. 134 at 16-17.

7 The Court begins with the claim language. Independent claim 1 of the ’187 Patent
8 in full recites:

9 1. A device for receiving and preserving nucleic acid in a biological sample,
10 said device comprising:

11 a. one or more walls defining a containment vessel having a top having an
12 opening, and a closed bottom having a sample receiving area for holding said
13 biological sample, said opening for receiving a liquid sample and for sealably
14 receiving a sealing cap, said top having an opening for receiving a biological
15 sample from the mouth of a user and further comprising at least one marking
16 on said one or more walls which corresponds to a fluid volume in the sample
17 receiving area;

18 b. a **reagent compartment** having a barrier, said barrier sealing and
19 containing reagents in said reagent compartment and capable of
20 disestablishment to release said reagents into the sample receiving area;

21 c. reagents in the **reagent compartment** for preserving nucleic acids
22 potentially present in the sample wherein said reagents comprise a denaturing
23 agent, a chelator and a buffer agent; and,

24 d. the sealing cap, whereby the device is configured such that, when sealably
25 closing said opening with said sealing cap, the barrier mechanically
26 disestablishes to release said reagents to form a mixture of reagents and said
27 biological sample wherein said buffering agent maintains a pH of said mixture
28

1 equal to or above 5.0 to preserve nucleic acids potentially present in the
2 sample.

3 '187 Patent col. 19 ll. 34-59 (emphasis added). Here, the claim language claims a device
4 comprising: (1) a containment vessel; (2) a sealing cap; (3) a reagent compartment; and (4)
5 reagents. But the claim language is ambiguous as to where precisely the reagent
6 compartment is located within the claimed device – whether it is in the containment vessel
7 or in the sealing cap or whether it can be in either.

8 Turning to the specification, the specification of the '187 Patent provides clear
9 guidance as to the location of the reagent compartment. The specification states:

10 In a sixth aspect, the invention features a device for preserving and/or isolating
11 a nucleic acid obtained from a biological sample. The device includes: a
12 container that has a first region for collecting a biological sample and a second
13 region containing a composition for preserving a nucleic acid, a barrier
14 between the first region the second region that keeps the biological sample
15 and the composition separate, a means for closing the container, and a means
16 for disturbing the integrity of the barrier such that the composition is capable
17 of contacting the biological sample.

18 '187 Patent col. 6 ll. 26-36; *see also id.* col. 6 ll. 6-14, col. 6 ll. 46-56, col. 14 ll. 30-35, col.
19 14 ll. 51-58. Here, the specification expressly and clearly states that the region containing
20 the composition for preserving a nucleic acid (*i.e.*, the reagent compartment) is located
21 within the container (*i.e.*, the collection vessel). *See id.* This strongly supports Spectrum's
22 proposed construction.

23 In response, DNA Genotek argues that it is improper to limit claims to a preferred
24 embodiment. ECF No. 134 at 17. But in the portion of the specification quoted above, the
25 specification is not describing a preferred embodiment. Rather, the specification is
26 describing the invention as a whole. *See* '187 Patent col. 6 ll. 26 (“the invention features .
27 . . .”); *see also id.* at col. 6 ll. 6 (same), col. 6 ll. 46 (same), col. 14 ll. 28 (same), col. 14 ll.
28

49 (same).¹² “When a patentee ‘describes the features of the ‘present invention’ as a whole,’ he implicitly alerts the reader that ‘this description limits the scope of the invention.’” *Luminara*, 814 F.3d at 1353 (quoting *Regents of Univ. of Minnesota*, 717 F.3d at 936); accord *Pacing*, 778 F.3d at 1025; see, e.g., *Wastow*, 855 F. App’x at 750–51; *Honeywell*, 452 F.3d at 1318. “The public is entitled to take the patentee at his word and the word was that the invention is a” device with a reagent compartment in the container. *Honeywell*, 452 F.3d at 1318; see also *Techtronic Indus. Co. v. Int’l Trade Comm’n*, 944 F.3d 901, 907 (Fed. Cir. 2019) (“It is axiomatic that, where the specification ‘describes “the present invention” as having [a] feature,’ that representation may disavow contrary embodiments.”); *Poly-Am.*, 839 F.3d at 1136 (“[A]n inventor may disavow claims lacking a particular feature when the specification describes “the present invention” as having that feature.”).

At the claim construction hearing, DNA Genotek argued that the passage quoted above is insufficient to constitute a disclaimer because it merely describes a “sixth aspect of many” of the invention. ECF No. 176 at 30. But all of the claims in the ’187 Patent claim a “device.” See ’187 Patent col. 19 ll. 34 to col. 21 ll. 17. In the specification, the “sixth aspect” of the invention is the only aspect of the invention that features “a device.” See *id.* col. 3 ll. 66 to col. 6 ll. 65 (describing the seven “aspects” of the invention).¹³ Further, as

¹² Indeed, in the cited portions of the specification, the specification uses express language to distinguish when it is describing “an embodiment” of the invention as opposed to “the invention” itself. Compare ’187 Patent col. 6 ll. 26 (“the invention features”), col. 14 ll. 49 (“the invention features”); with *id.* col. 6 ll. 40 (“In one embodiment of the sixth aspect”); col. 14 ll. 58 (“[i]n one embodiment”).

¹³ The Court notes that in addition to the “sixth aspect” of the invention described in the specification, the only other aspects of the invention described in the specification that disclose “a container” are the “fifth aspect” and the “seventh aspect.” The fifth aspect describes “a method of preserving and/or recovering a nucleic acid” utilizing a container. ’187 Patent col. 6 ll. 6-7. The specification expressly states that the container utilized by the fifth aspect of the invention has a reagent compartment in the container. See *id.* col. 6

DNA Genotek itself explained at the hearing, the “Detailed Description” section of the specification is broken up into three sub-sections: “Compositions of the Invention,” “Methods of the Invention,” and “Collection Devices.” ’187 Patent col. 9 ll. 1, col. 12 ll. 1, col. 14 ll. 39.¹⁴ The “Collection Devices” sub-section contains an almost identical disclaimer to the one quoted above. *See id.* at col. 14 ll. 49-54 (“Desirably, the invention features a device The device includes: a container that has a first region for collecting a biological sample and a second region containing a composition for preserving a nucleic acid, [and] a barrier between the first region the second region”). As such, this language in the specification constitutes a clear disclaimer explaining that when the claimed invention is a sample collection device (as opposed to a composition or a method),

ll. 10-11 (“placing a composition of the invention into a second region of the container, which is separated from the first region by a barrier”).

The seventh aspect of the invention is directed to “a method of manufacturing a device” that includes “a container.” *Id.* col. 6 ll. 46-48. The specification expressly states that the container utilized by the seventh aspect of the invention has a reagent compartment in the container. *See id.* col. 6 ll. 10-11 (“providing a container that has a first region and a second region, with the first region suitable for containing a composition of the invention”).

In sum, the fifth, sixth, and seventh aspects of the invention are the only aspects of the invention in the specification that disclose a container (*i.e.*, a containment vessel) and a region for containing a composition of the invention (*i.e.*, a reagent compartment). *See* ’187 Patent col. 6 ll. 6-14, col. 6 ll. 26-36, col. 6 ll. 46-56. And those three aspects of the invention all expressly state that the reagent compartment is in the container. *Id.* There is no explicit disclosure of a reagent compartment that is located anywhere else other than in the container. *See id.*; *see also id.* at figs. 10, 11, col. 8 ll. 46-54, col. 14 ll. 28-35, col. 14 ll. 51-58, col. 15 ll. 17-29, col. 15 ll. 33-49.

¹⁴ “Section 101 [of the Patent Act] specifies four independent categories of inventions or discoveries that are eligible for protection: processes [(*e.g.*, methods)], machines, manufactures [(*e.g.*, devices)], and compositions of matter.” *Bilski v. Kappos*, 561 U.S. 593, 601 (2010). A claimed invention must fit within at least “one of the four statutorily provided categories of patent-eligible subject matter.” *Aatrix Software, Inc. v. Green Shades Software, Inc.*, 882 F.3d 1121, 1125 (Fed. Cir. 2018) (quoting *Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 713–14 (Fed. Cir. 2014); *Digitech Image Techs., LLC v. Elecs. for Imaging, Inc.*, 758 F.3d 1344, 134850 (Fed. Cir. 2014)).

1 the reagent compartment is in the container of the device and not in alternative locations.
 2 *See, e.g., Techtronic*, 944 F.3d at 908 (“[B]y consistently representing the invention as the
 3 placement of the detector in the wall console, [the specification] has thus effected a
 4 disavowal of alternative locations.”).¹⁵

5 DNA Genotek argues that Spectrum’s proposed construction is improper because it
 6 would read out a disclosed embodiment from the scope of the claims. ECF No. 134 at 17-
 7 18. The ’187 Patent claims priority to and expressly incorporates by reference the ’398
 8 Provisional. ’187 Patent col. 1 ll. 16-19. The Federal Circuit has explained: “provisional
 9 applications incorporated by reference are ‘effectively part of the’ specification as though
 10 it was ‘explicitly contained therein.’” *Trs. of Columbia Univ. in City of New York v.*
 11 *Symantec Corp.*, 811 F.3d 1359, 1366 (Fed. Cir. 2016) (quoting *Advanced Display Sys.,*
 12 *Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)); *see also MPHJ Tech. Invs.,*
 13 *LLC v. Ricoh Americas Corp.*, 847 F.3d 1363, 1369 (Fed. Cir. 2017) (“[A] provisional
 14 application can contribute to understanding the claims.”).¹⁶ The ’398 Provisional contains
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16
 17 ¹⁵ The Court acknowledges that the Federal Circuit has explained that use of the phrase
 18 “present invention” or “this invention” is not always limiting, “such as where the
 19 references . . . are not uniform, or where other portions of the intrinsic evidence do not
 20 support applying the limitation to the entire patent.” *Cont’l Cirs. LLC v. Intel Corp.*, 915
 21 F.3d 788, 798 (Fed. Cir. 2019) (quoting *Absolute Software, Inc. v. Stealth Signal, Inc.*, 659
 22 F.3d 1121, 1136–37 (Fed. Cir. 2011)). But neither of those scenarios is present here. As
 23 explained above, every explicit disclosure of a sample collection device in the specification
 24 is one where the device has a reagent compartment in the container and nowhere else. *See,*
 25 *e.g., ’187 Patent col. 6 ll. 6-14, col. 6 ll. 26-36, col. 6 ll. 46-56, col. 14 ll. 49-54; see also*
 26 *supra* note 13.

27 ¹⁶ Spectrum argues that incorporation by reference of a provisional application is
 28 ineffective because a provisional application is not a U.S. patent or U.S. patent application
 publication, citing 37 C.F.R. § 1.57(d), *ZTE (USA), Inc. v. Cywee Group. Ltd.*, No.
 IPR2019-00143, 2021 WL 641742, at *54 (P.T.A.B. Feb. 17, 2021), and *Nomadix, Inc. v.*
Second Rule LLC, No. CV0701946DDPVBKX, 2009 WL 10668158, at *24 (C.D. Cal.
 Jan. 16, 2009). ECF No. 88 at 6-7. 37 C.F.R. § 1.57(d) provides: “‘Essential material’ may
 be incorporated by reference, but only by way of an incorporation by reference to a U.S.
 patent or U.S. patent application publication.” *Accord Droplets, Inc. v. E*TRADE Bank,*

1 an embodiment where the reagent compartment is in the cap. *See* ECF No. 83-7, Ex. 6 at
2 p. 260 ll. 12-13, p. 262 ll. 4-9, p. 266 fig. 2. DNA Genotek argues that Spectrum’s proposed
3 construction would exclude this specific embodiment. ECF No. 134 at 17-18. “A claim
4 construction that excludes a preferred embodiment is rarely, if ever correct and would

5 _____
6 887 F.3d 1309, 1318 (Fed. Cir. 2018). In *ZTE*, the PTAB explained: “Because a U.S.
7 provisional application is not a ‘U.S. patent or U.S. patent application publication,’” the
8 application at issue’s attempt to incorporate by reference a “provisional application was
9 ineffective.” 2021 WL 641742, at *54.

10 Although the Court finds that Spectrum’s argument has merit, it is primarily based
11 on a non-binding PTAB decision and a non-binding district court decision. The Court is
12 bound by the Federal Circuit’s decision in *Trustees of Columbia University*. *See Panduit*
13 *Corp. v. All States Plastic Mfg. Co.*, 744 F.2d 1564, 1573 (Fed. Cir. 1984) (explaining that
14 district courts are “bound by the substantive patent law of” the Federal Circuit); *see, e.g.,*
15 *In re Micron Tech., Inc.*, 875 F.3d 1091, 1098 (Fed. Cir. 2017) (“On the patent-specific
16 issue of the proper interpretation of 28 U.S.C. § 1400(b), the district court was bound by
17 this court’s precedent.”); *see also Yong v. I.N.S.*, 208 F.3d 1116, 1119 (9th Cir. 2000)
18 (“once a federal circuit court issues a decision, the district courts within that circuit are
19 bound to follow it”).

20 At the claim construction hearing, Spectrum noted that in *Trustees of Columbia*
21 *University*, the Federal Circuit did not expressly address 37 C.F.R. § 1.57(d) in holding
22 that provisional applications incorporated by reference are effectively part of the
23 specification. ECF No. 176 at 43-44. This is true. *See Trs. of Columbia Univ.*, 811 F.3d at
24 1365–66. And this is an additional reason why Spectrum’s argument has merit. In addition,
25 the Court notes that in *Trustees of Columbia University*, to support its contention that a
26 provisional application incorporated by reference effectively becomes part of the
27 specification, the court cited to the Federal Circuit’s decision in *Advanced Display*. *See*
28 *Trs. of Columbia Univ.*, 811 F.3d at 1366. In *Advanced Display*, the Federal Circuit
describes the standards for evaluating whether and to what extent material has been
incorporated by reference into a host document. *See* 212 F.3d at 1282–84. But the
Advanced Display decision never expressly references provisional applications or 37
C.F.R. § 1.57(d). *See id.*

Nevertheless, the Court also notes that the Federal Circuit in at least one subsequent
decision has acknowledged and cited favorably to *Trustees of Columbia University*’s use
of a provisional application for claim construction purposes. *See MPHJ*, 847 F.3d at 1369.
As such, the Court remains bound by the Federal Circuit’s holding in *Trustees of Columbia*
University. *See Panduit*, 744 F.2d at 1573; *Micron*, 875 F.3d at 1098.

1 require highly persuasive evidentiary support.” *Kaufman*, 34 F.4th at 1372. But, here, there
 2 is highly persuasive evidentiary support for Spectrum’s proposed construction and
 3 Spectrum’s contention that the reagent compartment must be in the containment vessel.

4 First, in *Finjan LLC v. ESET, LLC*, the Federal Circuit explained that “the disclosure
 5 of the host patent provides context to determine what impact, if any, a [document]
 6 incorporated by reference will have on construction of the host patent claims.” 51 F.4th
 7 1377, 1382 (Fed. Cir. 2022) (citing *X2Y Attenuators, LLC v. U.S. Int’l Trade Comm’n*, 757
 8 F.3d 1358, 1362–63 (Fed. Cir. 2014)); *see also Advanced Display*, 212 F.3d at 1283
 9 (“Whether and to what extent material has been incorporated by reference into a host
 10 document is a question of law.”). Here, as noted above, the specification as issued contains
 11 several disclaimers of claim scope expressly stating that the disclosed invention features a
 12 device with a reagent compartment that is located in the container. *See* ’187 Patent col. 6
 13 ll. 6-14, col. 6 ll. 26-36, col. 6 ll. 46-56, col. 14 ll. 49-54. In light of this language, the
 14 specification “disavow[s] contrary embodiments,” including those disclosed in the ’398
 15 Provisional. *Techtronic*, 944 F.3d at 907; *see, e.g., Finjan*, 51 F.4th at 1382–83 (declining
 16 to apply definition from patent incorporated through reference into the specifications at
 17 issue based on the context provided by the language in those specifications).

18 Second, as Spectrum correctly notes, when the patentee filed its non-provisional
 19 application, it deleted any explicit disclosure of the reagent compartment being in the
 20 cap/lid.¹⁷ The Federal Circuit in *MPHJ* held that the deletion of material from a provisional

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 22
 23 ¹⁷ At the claim construction hearing, DNA Genotek challenged the Court’s
 24 characterization of the removal of material from the ’398 Provisional as being a “deletion”
 25 of that material. *See* ECF No. 176 at 17 (“So to say that something was deleted out of that
 26 just isn’t a correct description of how provisional applications work.”). The Court notes
 that the Federal Circuit in *MPHJ* referred to certain statements in a provision application
 that were omitted from the final application as being a “deletion.” 847 F.3d at 1369.

27 At the claim construction hearing, DNA Genotek also noted that some components
 28 of the embodiment at issue in the ’398 Provisional were retained in the ’187 Patent’s
 specification, such as the “septum” and the “piercing member.” *See* ECF No. 176 at 19-21;

1 application can contribute to the understanding of the intended scope of the final
2 application. 847 F.3d at 1369; *see also Finjan*, 51 F.4th at 1383 (“The use of a restrictive
3 term in an earlier application does not reinstate that term in a later patent that purposely
4 deletes the term, even if the earlier patent is incorporated by reference.”).¹⁸ And, notably,
5 the Federal Circuit in *MPHJ* held this despite the provisional application at issue in that
6 case being expressly incorporated by reference into the specification. *See* 847 F.3d at 1371.
7 As such, here, the patentee’s deletion of any explicit disclosure of the reagent compartment
8 being in is the cap/lid along with the disclaimers in the issued version of the specification
9

10
11 *see, e.g.*, ’187 Patent col. 15 ll. 17-20, col. 20 ll. 7-12, col. 21 ll. 13-17. But this is of no
12 consequence. The issue is not whether the specification as issued retained any components
13 from the embodiment at issue in the ’398 Provisional. Rather, the issue is whether the
14 specification retained any explicit disclosure of a reagent compartment that is in the cap/lid.
15 DNA Genotek has not identified any passage in the specification of the ’187 Patent that
16 explicitly discloses a reagent compartment that is located in the cap/lid. *See also supra* note
17 13.

18 ¹⁸ DNA Genotek argues that the Federal Circuit’s decision in *MPHJ* is irrelevant here
19 because that case involved the “broadest reasonable interpretation” standard for claim
20 construction. ECF No. 89 at 8-9. The Court acknowledges that the “broadest reasonable
21 interpretation” standard that was previously applied by the PTAB during IPR proceedings
22 is different from the *Phillips* standard for claim construction applied by district courts. *See*
23 *Seabed Geosolutions*, 8 F.4th at 1287 (recognizing the difference between the two
24 standards). But DNA Genotek fails to adequately explain how that difference between the
25 two standards affects the applicability of *MPHJ*’s general holding that deletion of material
26 from a provisional application can contribute to the “understanding of the intended scope
27 of the final application.” 847 F.3d at 1369. The Court notes that in reaching that holding,
28 the panel in *MPHJ* cited to its prior decisions in *Trustees of Columbia University* and
Vederi, which are both cases applying the *Phillips* standard of claim construction. *See*
MPHJ, 847 F.3d at 1369 (citing *Trustees of Columbia Univ.*, 811 F.3d at 1365; *Vederi*,
LLC v. Google, Inc., 744 F.3d 1376, 1383 (Fed. Cir. 2014)); *see also Trustees of Columbia*
Univ., 811 F.3d at 1362–63 (setting forth the *Phillips* standard for claim construction);
Vederi, 744 F.3d at 1382 (same); *see also, e.g., CXT Sys., Inc. v. Acad., Ltd.*, No.
218CV00171RWSRSP, 2019 WL 4253841, at *17 n.20 (E.D. Tex. Sept. 6, 2019)
(rejecting defendants’ argument “that *MPHJ* is distinguishable in that it was applying the
broadest-reasonable-interpretation standard”).

1 explaining that the reagent compartment is in the container evidence a clear intent to limit
2 the final scope of the invention to a device with the reagent compartment in the containment
3 vessel.¹⁹ *See id.* at 1369.

4 Third, Spectrum has cited to highly persuasive extrinsic evidence supporting the
5 notion that the invention disclosed in the '187 Patent is limited to a device where the
6 reagent compartment is specifically located in the container and not the cap/lid. During
7 IPR proceedings as to a different patent owned by DNA Genotek, U.S. Patent No.
8 8,221,381 ("the '381 Patent"), in an effort to sustain the validity of the '381 Patent, DNA
9 Genotek described the teachings and scope of the invention disclosed in the '187 Patent.
10 DNA Genotek stated (referring to the invention disclosed in the '187 Patent as
11 "Birnbom"):

12 Technically, O'Donovan and Birnbom are very different devices.

13 O'Donovan is a pushed friction fit engagement with spikes in a vial and a
14 reagent in a lid, where the vial includes a shoulder to support the spikes and
15 facilitate rupturing a pierceable membrane in the lid to release the reagent.

18 ¹⁹ Although the Court finds the Federal Circuit's holding in *MPHJ* to be applicable
19 here, the Court notes that it disagrees with Spectrum's interpretation of *MPHJ*. Spectrum
20 argues that under the Federal Circuit's decision in *MPHJ*, the deletion of material from a
21 provisional application by itself can constitute a disavowal of claim scope. *See* ECF No.
22 147 at 14-17; ECF No. 88 at 6. The Court disagrees. There is nothing in *MPHJ* stating that
23 the mere deletion of material from a provisional application can constitute a disavowal of
24 claim scope. *Cf. Poly-Am.*, 839 F.3d at 1136 ("[T]he standard for disavowal is exacting,
requiring clear and unequivocal evidence that the claimed invention includes or does not
include a particular feature.").

25 As such, the Court makes clear that it does not find that the deletion of the disclosures
26 at issue from the '398 Provisional alone constitutes a disavowal of claim scope. Rather, the
27 Court merely finds that the deletion of any disclosure of an embodiment where the reagent
28 compartment in is the cap/lid is consistent with and supports the disclaimers contained in
the '187 Patent's specification as issued explaining that the reagent compartment is in the
container.

1 Birnboim is a rotated screw cap with a ram in the cap and a reagent below a
2 plastic cover in a container, where the ram forces a push rod to flip the plastic
3 and thereby expose a sample to the reagent.

4 ECF No. 83-10, Ex. 9 at 326-27 (citations omitted); *see also* U.S. Patent No. 8,221,381
5 col. 1, ll. 50-59 (describing the invention claimed in the '187 Patent and stating "[t]h[e]
6 container has a first region for collecting a biological sample, a second region containing a
7 composition for preserving a nucleic acid, and a barrier between the first region and the
8 second region"). Here, DNA Genotek described the scope of its own invention, the
9 invention disclosed in the '187 Patent, as being a device where the reagent is contained in
10 the container, and DNA Genotek further stated that the disclosed device is "very different"
11 from a device where the reagent is in a lid.²⁰ The Court notes that these statements by DNA
12 Genotek are highly relevant to claim construction as "the statements were 'made in an
13 official proceeding in which the patentee had every incentive to exercise care in
14 characterizing the scope of its invention.'" *Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286,
15 1313 (Fed. Cir. 2014), *overruled on other grounds by Williamson v. Citrix Online, LLC*,
16 792 F.3d 1339 (Fed. Cir. 2015) (quoting *Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d
17 1340, 1350 (Fed. Cir. 2004)).

18 At the claim construction hearing, DNA Genotek argued that its statements during
19 the IPR proceedings at issue are irrelevant for claim construction purposes because the
20 patent at issue in the IPR proceedings, the '381 Patent, is unrelated to the '187 Patent. ECF
21 No. 176 at 25-26 (citing *Apple*, 757 F.3d at 1312). The Court acknowledges that
22 "statements made in unrelated applications are not relevant to claim construction." *Apple*,
23

24
25 ²⁰ DNA Genotek argues that the above statement was made in reference to an
26 embodiment of the '187 Patent. ECF No. 89 at 9. The Court rejects this argument. Although
27 at times in the response brief, DNA Genotek expressly refers to embodiments of the '187
28 Patent, *see, e.g.*, ECF No. 83-10, Ex. 9 at 319-20, in the passage cited above, DNA Genotek
does not use any language explaining that it is merely referring to a preferred embodiment
of the invention rather than the invention disclosed in the '187 Patent as a whole.

1 757 F.3d at 1312. But the statements at issue are not mere statements made in an unrelated
2 application. Rather, they are statements by the patentee about the scope of its own invention
3 in an official proceeding, represented by counsel, in an effort to preserve the validity of
4 another one of its patents. There are many good reasons why these statements are and
5 should be relevant for claim construction purposes. The Federal Circuit has explained that
6 the public and the Court are “entitled to take the patentee at his word” regarding the scope
7 of its invention. *Microsoft*, 357 F.3d at 1350; *Honeywell*, 452 F.3d at 1318. In addition, the
8 Federal Circuit has explained that competitors should be “entitled to rely on [a patentee’s]
9 representations when determining a course of lawful conduct, such as launching a new
10 product or de-signing-around a patented invention.” *Aylus*, 856 F.3d at 1359. And the
11 Federal Circuit has explained that “one cannot interpret a patent one way for the validity
12 analysis and a different way for the infringement analysis.” *A. G. Design & Assocs. LLC v.*
13 *Trainman Lantern Co.*, 271 F. App’x 995, 999 (Fed. Cir. 2008); *see Data Engine*, 10 F.4th
14 at 1381 (“We have repeatedly rejected efforts to twist claims, like a nose of wax, in one
15 way to avoid [invalidity] and another to find infringement.” (internal quotation marks
16 omitted)); *Aylus*, 856 F.3d at 1360 (explaining that claims should not be “construed one
17 way in order to obtain their allowance and in a different way against accused infringers”).

18 At the claim construction hearing, DNA Genotek also argued that the Court should
19 not give weight to its statements in the IPR proceedings because claim construction of the
20 ’187 Patent was not at issue during the IPR proceedings regarding the ’381 Patent. ECF
21 No. 176 at 26-27. The Court acknowledges that the proper interpretation of the claims of
22 the ’187 Patent was not at issue during the IPR proceedings.²¹ But the scope of the
23 invention disclosed in the ’187 Patent was at issue in the IPR proceedings, and, therefore,
24 DNA Genotek’s statements are probative for claim construction purposes.

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27
28 ²¹ Indeed, the ’187 Patent had not even issued at the time of the IPR proceedings.

1 During the IPR proceedings, Birnboim (the invention disclosed in the '187 Patent)
2 was being used as a prior art reference in an attempt to render the '381 Patent invalid as
3 obvious under 35 U.S.C. § 103. ECF No. 83-10, Ex. 9 at 288, 314. An obviousness
4 determination requires, among other things, an analysis of “the scope and content of the
5 prior art,” *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1047 (Fed. Cir. 2016) (en
6 banc), and, specifically, “requires finding that a person of ordinary skill in the art would
7 have been motivated to combine or modify the teachings in the prior art” *Adapt*
8 *Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1365 (Fed. Cir. 2022).
9 In arguing that Spectrum failed to demonstrate motivation to combine or modify, DNA
10 Genotek made certain statements regarding the differences between the teachings in
11 Birnboim and the teachings in the other prior art reference at issue, O'Donovan. *See* ECF
12 No. 83-10, Ex. 9 at 326-27; *cf. Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir.
13 2020) (“Fundamental differences between the references are central to this motivation to
14 combine inquiry.”). Thus, the scope of the teachings in Birnboim (*i.e.*, the scope of its
15 disclosure) was directly at issue during the relevant IPR proceedings and in the statements
16 made by DNA Genotek. *Cf. Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069
17 (Fed. Cir. 2018) (explaining that in an obviousness analysis a prior art reference “must
18 [be] considered for all it taught” through its “disclosures”) (quoting *Ashland Oil, Inc. v.*
19 *Delta Resins & Refractories, Inc.*, 776 F.2d 281, 296 (Fed. Cir. 1985)). Further, the claims
20 of the '187 Patent may not be broader in scope than that disclosure. *See Gentry Gallery,*
21 *Inc. v. Berkline Corp.*, 134 F.3d 1473, 1480 (Fed. Cir. 1998) (“[C]laims may be no broader
22 than the supporting disclosure, and therefore that a narrow disclosure will limit claim
23 breadth.”); *Indacon, Inc. v. Facebook, Inc.*, 824 F.3d 1352, 1357 (Fed. Cir. 2016) (“[Claim
24 terms] ordinarily cannot be construed broader than the disclosure in the specification.”).

1 As such, DNA Genotek’s statements even if extrinsic evidence are highly relevant for
2 claim construction purposes here.²²

3 In sum, the specification of the ’187 Patent contains several clear disclaimers
4 explaining that the invention claimed in the ’187 Patent features a device with the reagent
5 compartment in the container (*i.e.*, the containment vessel). Those disclaimers in the
6 specification are supported by the deletion of any explicit disclosure of the reagent
7 compartment being in the cap/lip from the ’398 Provisional and by DNA Genotek’s
8 statements during IPR proceedings describing the scope of the claimed invention. As a
9 result, the Court adopts Spectrum’s proposed construction for this claim term. The Court
10 construes the term “reagent compartment” as “region or section of the containment vessel.”

11 //

12 //

13 //

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25
26 ²² In briefing, Spectrum expressly states that it does not contend that Genotek’s
27 statements during the IPR proceedings as to the ’381 Patent constitute estoppel. ECF No.
28 147 at 19. The Court agrees with Spectrum that the statements at issue are insufficient to
constitute estoppel. Nevertheless, they are relevant to claim construction, and they support
Spectrum’s proposed construction for the claim term “reagent compartment.”

E. “when sealably closing said opening with said sealing cap, the barrier mechanically disestablishes”

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
The term does not require construction and should be accorded plain and ordinary meaning.	This term is governed by 35 U.S.C. § 112, ¶ 6 (pre-AIA) Corresponding structure: “a cap having a ram and a plunger” Function “mechanically disestablishing the barrier upon sealably closing the opening of the sample receiving area”	Plain and ordinary meaning.

Here, the Parties dispute whether the claim term “when sealably closing said opening with said sealing cap, the barrier mechanically disestablishes” is a means-plus-function claim element that is governed by pre-AIA § 112 ¶ 6. Spectrum argues that the claim term at issue is a means-plus-function claim element because the claim language fails to recite sufficient structure for performing the claimed function of disestablishment of the barrier. ECF No. 147 at 22-26. In response, DNA Genotek argues that Spectrum’s arguments are insufficient to rebut the presumption that the claim term at issue is not a means-plus-function claim term. ECF No. 89 at 10-11.

“Means-plus-function claiming occurs when a claim term is drafted in a manner that invokes § 112, para. 6.” *Diebold Nixdorf, Inc. v. Int’l Trade Comm’n*, 899 F.3d 1291, 1297 (Fed. Cir. 2018); *see also Dyfan, LLC v. Target Corp.*, 28 F.4th 1360, 1365 (Fed. Cir. 2022) (“Limitations that invoke § 112 ¶ 6 are generally known as ‘means-plus-function’ or ‘step-plus-function’ limitations.”). Section 112 ¶ 6 of the Patent Act provides:

1 An element in a claim for a combination may be expressed as a means or step
 2 for performing a specified function without the recital of structure, material,
 3 or acts in support thereof, and such claim shall be construed to cover the
 4 corresponding structure, material, or acts described in the specification and
 5 equivalents thereof.

6 35 U.S.C. § 112 ¶ 6 (pre-AIA); *accord* 35 U.S.C. § 112(f) (current).²³ In enacting this
 7 provision, Congress “‘struck a balance in allowing patentees to express a claim limitation
 8 by reciting a function to be performed rather than by reciting structure for performing that
 9 function,’ while ‘placing specific constraints on how such a limitation is to be construed’—
 10 that is, by restricting the ‘scope of coverage to only the structure, materials, or acts
 11 described in the specification as corresponding to the claimed function and equivalents
 12 thereof.’” *Diebold Nixdorf*, 899 F.3d at 1297 (quoting *Williamson v. Citrix Online, LLC*,
 13 792 F.3d 1339, 1347 (Fed. Cir. 2015) (en banc)).

14 “The overall means-plus-function analysis is a two-step process.” *Dyfan*, 28 F.4th at
 15 1365. “The first step is to determine whether a claim limitation is drafted in means-plus-
 16 function format, which requires [the court] to construe the limitation to determine whether
 17 it connotes sufficiently definite structure to a person of ordinary skill in the art.” *Id.* “If the
 18 limitation connotes sufficiently definite structure, it is not drafted in means-plus-function
 19 format, and § 112 ¶ 6 does not apply.” *Id.* If, however, the court concludes that the
 20 limitation is in means-plus-function format, the court performs the second step of
 21 “determining ‘what structure, if any, disclosed in the specification corresponds to the
 22 claimed function.’” *Id.* (quoting *Williamson*, 792 F.3d at 1351).

23 “If the limitation uses the word ‘means,’ there is a rebuttable presumption that § 112
 24 ¶ 6 applies.” *Rain Computing, Inc. v. Samsung Elecs. Am., Inc.*, 989 F.3d 1002, 1005 (Fed.
 25

26
 27 ²³ The Court notes that the above language in paragraph 6 of the pre-AIA version of §
 28 112 is identical to the language in current § 112(f). *See* 35 U.S.C. § 112(f).

1 Cir. 2021). “If not, there is a rebuttable presumption that the provision does not apply.” *Id.*
2 But “the presumption can be overcome and § 112, para. 6 will apply if the challenger
3 demonstrates that the claim term fails to ‘recite sufficiently definite structure’ or else recites
4 ‘function without reciting sufficient structure for performing that function.’” *Williamson*,
5 792 F.3d at 1349. “Whether claim language invokes 35 U.S.C. § 112 ¶ 6 is a question of
6 law.” *Rain*, 989 F.3d at 1005.

7 The Court begins with the claim language. The limitation at issue, the claim term
8 “when sealably closing said opening with said sealing cap, the barrier mechanically
9 disestablishes,” does not use the word “means.” *See* ’187 Patent col. 19 ll. 54-55. As such,
10 there is a rebuttable presumption that § 112 ¶ 6 does not apply. *See Rain*, 989 F.3d at 1005.
11 In order to rebut that presumption, Spectrum must demonstrate that claim term fails to
12 recite sufficiently definite structure or else recites function without reciting sufficient
13 structure for performing that function. *See Williamson*, 792 F.3d at 1349; *Rain*, 989 F.3d
14 at 1005.

15 In an effort to rebut the presumption, Spectrum argues that the claim language
16 “recites the function of mechanically disestablishing the barrier to release the reagents, but
17 the claim does not identify any structure for performing that function.” ECF No. 147 at 22.
18 But Spectrum fails to properly view the claim term at issue within the context of the
19 surrounding claim language. The claim term at issue is contained within section “d.” of
20 independent claim 1 which recites: “the sealing cap, whereby the device is configured such
21 that, when sealably closing said opening with said sealing cap, the barrier [of the reagent
22 compartment] mechanically disestablishes to release said reagents to form a mixture of
23 reagents and said biological sample” ’187 Patent col. 19 ll. 53-57. Here, the claim
24 language identifies “the sealing cap” as the structure that performs the function of
25 mechanically disestablishing the barrier. As such, the claim language provides sufficient
26 structure for the claimed function of mechanically disestablishing the barrier.

27 Spectrum argues that the claim language only identifies the “sealing cap” as the
28 structure that performs the function of sealably closing the container’s opening, but there

1 is no structure identified for mechanically disestablishing the barrier. ECF No. 147 at 24.
 2 Spectrum’s contention is based on a misunderstanding of the claim language. The claim
 3 language identifies “the sealing cap” as the structural component of the device that
 4 performs both the function of sealably closing the container’s opening and the function of
 5 mechanically disestablishing the barrier. *See* ’187 Patent col. 19 ll. 53-57.

6 That the sealing cap performs both of these functions is further supported by a review
 7 of the specification. The specification explains: “In one embodiment, the disestablishment
 8 of the barrier is coupled to the closing of the container when a lid is placed on it. In one
 9 example, the barrier is punctured. In a desirable example, the barrier is in the form of a
 10 pivoting sealing disc. In this example, attachment of the lid to the container forces the disc
 11 to pivot” ’187 Patent col. 6 ll. 15-20. Here, the specification describes an embodiment
 12 of the invention where the lid (*i.e.*, the cap) of the device performs both the closing of the
 13 container and the disestablishment of the barrier.²⁴ Additionally, the specification states:
 14 “the means for closing the container may be coupled to the disestablishment of the barrier.”
 15 *Id.* at col. 15 ll. 29-30; *see also id.* col. 15 ll. 11 (“the means for closing the container may
 16 be a cap”). Here, the specification explains that the means for closing the container (*e.g.*, a
 17 cap) can also perform the disestablishment of the barrier. Thus, the specification supports
 18 the notion that by reciting a “sealing cap” the claim language provides sufficient structure
 19 for the claimed function of mechanically disestablishing the barrier.²⁵

24 The Court notes that this particular embodiment does not reference “a cap with a
 ram and a plunger.” *See generally* ’187 Patent col. 6 ll. 6-24. As such, this contradicts
 Spectrum’s contention that the only disclosure in the specification of structure that
 mechanically disestablishes the barrier “is ‘a cap having a ram, and a plunger.’” ECF No.
 147 at 26.

25 Spectrum argues that the disclosure of a sealing cap is insufficient because:
 “although most collection devices have a sealing cap, these structures do not normally
 include any apparatus to mechanically disestablish a barrier.” ECF No. 147 at 25. Spectrum
 does not support this assertion with a citation to any evidence, intrinsic or extrinsic.

1 A review of the prosecution history also supports the conclusion that the claim term
 2 at issue is not a means-plus-function claim element. As originally drafted claim 1 (formerly
 3 claim 30) recited “**closing means** and **disruptions means**, said **disruption means** for
 4 engaging said barrier whereby when sealably closing said opening with said closing means,
 5 said **disrupting means** mechanically disestablishes said barrier to release said reagents.”
 6 ECF No. 83-4, Ex. 3 at 95 (emphasis added) (deleted material omitted). The Examiner
 7 recognized the claim as invoking means-plus-function claiming and rejected the claim as
 8 indefinite for failing to “clearly link or associate the disclosed structure, material, or acts
 9 to the claimed function such that one of ordinary skill in the art would recognize what
 10 structure, material, or acts perform the claimed function of the ‘disruption means.’” *Id.* at
 11 89. In response, the patentee amended the claim as follows, removing the terms “closing
 12 means” and “disruption means” from the claim language:

13 d. the sealing cap, ~~closing means and disruptions means~~, said ~~disruption~~
 14 ~~means for engaging said barrier~~ whereby the device is configured such that,
 15 when sealably closing said opening with said sealing cap ~~closing means~~, the
 16 barrier ~~said disrupting means~~ mechanically disestablishes ~~said barrier~~ to
 17 release said reagents

18 *Id.* at 71 (new language underlined in original). In addition, patentee stated: “Applicant
 19 amends the claims per the Examiner’s suggestion, so that the claim no longer includes
 20 means plus function limitations.” *Id.* at 84 (underlining in original). The PTO accepted the
 21 claim as amended. *See* ECF No. 134-20, Ex. 15 at 334, 338-41. Here, the patentee’s
 22 amendment of the claims to remove the means-plus-function limitations evidences an
 23 intent for the claim term at issue to avoid the application of § 112, ¶ 6. *See, e.g., TEK Glob.,*
 24 *S.R.L. v. Sealant Sys. Int’l, Inc.*, 920 F.3d 777, 786 (Fed. Cir. 2019) (determining that the
 25 prosecution history establishes that the applicant intended for the claim term at issue to
 26 avoid the application of § 112, ¶ 6).

27 Spectrum argues that the prosecution history actually supports its contention that the
 28 claim term is a means-plus-function claim because when the patentee amended the claim,

1 it only added the “sealing cap” as the structure for performing the function of the “closing
 2 means,” but the patentee did not add any structure for performing the function of the
 3 “disruption means.” ECF No. 147 at 24-25; ECF No. 88 at 9. This argument is based on
 4 Spectrum’s faulty premise that the claimed “sealing cap” can only perform one of the
 5 claimed functions at issue. The specification makes clear that the sealing cap can perform
 6 both the closing of the container and the disestablishment of the barrier.²⁶

7 In sum, a review of the intrinsic record demonstrates that the claimed “sealing cap”
 8 provides sufficient structure for the claimed function of mechanically disestablishing the
 9 barrier. As such, Spectrum has failed to rebut the presumption that the claim term “when
 10 sealably closing said opening with said sealing cap, the barrier mechanically
 11 disestablishes” is not a means-plus-function claim element, and, thus, the Court holds that
 12 the claim term is not a means-plus-function claim element.

13 Spectrum does not provide an alternative proposed construction for this claim term
 14 absent means-plus-function claiming. *See* ECF No. 147 at 20. And DNA Genotek argues
 15 that the Court need not construe the claim term and instead the term should be given its
 16

17 ²⁶ At the claim construction hearing, Spectrum also tried to advance a narrative where
 18 DNA Genotek responded to the examiner’s rejection purportedly by amending the claim
 19 language to remove the “closing means” as a means-plus function limitation, retaining the
 20 “disruption means” limitation as means-plus function limitation, and citing corresponding
 21 structure to the examiner to provide support for the “disruption means” as means-plus
 22 function limitation. *See* ECF No. 176 at 55-60. But Spectrum’s narrative is simply not
 23 supported by the record. In the response at issue, DNA Genotek expressly states to the
 24 examiner: “Applicant amends the claims . . . , so that the claim no longer includes means
 25 plus function limitations.” ECF No. 83-4, Ex. 3 at 84 (underlining in original). Here, DNA
 26 Genotek expressly refers to “means plus function limitations” (plural), making it clear that
 27 it was removing both the “closing means” and the “disruption means” and any other means-
 28 plus-function claim limitations from the claim language. Further, the Court notes that in
 the response at issue, one of the citations made by DNA Genotek to identify corresponding
 structure is to the embodiment in the specification where the lid/cap of the container
 performs the disestablishment of the barrier. *See id.* (citing paragraph “[0029]”); U.S.
 Patent App. No. 2017/0152545, at [0029] (filed Jun. 1, 2017), *available at*
<https://patents.google.com/patent/US20170152545A1/en?q=US+2017%2f0152545>.

plain and ordinary meaning. *See* ECF No. 134 at 18. In light of this, the Court gives the claim term “when sealably closing said opening with said sealing cap, the barrier mechanically disestablishes” its plain and ordinary meaning, and the Court declines to construe the claim term. *See Eon*, 815 F.3d at 1318 (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”).

F. “linear actuator”

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
“a device that converts linear motion into rotational motion and/or vice-versa”	Indefinite. In the alternative, “a cap having a ram, and a plunger”	“a device that converts rotational motion into linear motion”

DNA Genotek proposes that the claim term “linear actuator” be construed as “a device that converts linear motion into rotational motion and/or vice-versa.” ECF No. 134 at 12. Spectrum argues that DNA Genotek’s proposed construction would render dependent claims 21 and 26 of the ’187 patent invalid for failure to comply with 35 U.S.C. § 112 ¶ 4 (pre-AIA). ECF No. 147 at 26-27; ECF No. 88 at 10.²⁷ In the alternative,

²⁷ DNA Genotek argues that Spectrum waived this invalidity argument by failing to disclose it in Spectrum’s February 4, 2022 amended invalidity contentions. ECF No. 134 at 12 n.2; ECF No. 89 at 11-12. Patent Local Rule 3.3(d) requires a party’s “Invalidity Contentions” to set forth “[a]ny grounds of invalidity based on indefiniteness under 35 U.S.C. § 112(2) of any of the asserted claims.” S.D. Cal. Pat. L.R. 3.3(d). But, here, Spectrum’s invalidity argument is based on § 112 ¶ 4, not § 112 ¶ 2. *See* ECF No. 147 at 27. As such, Spectrum did not violate the Court’s Patent Local Rules by failing to set forth this particular invalidity argument in its amended invalidity contentions. Moreover, the Court notes that Spectrum set forth its contention that the claim term “linear actuator” is indefinite, rendering dependent claims 21 and 26 invalid, in the Parties’ January 7, 2022 Joint Claim Construction Chart and Worksheet, well in advance of the deadlines in this case for claim construction discovery and claim construction briefing. *See* ECF No. 74-1

1 Spectrum proposes that the claim term “linear actuator” be construed as “a cap having a
2 ram, and a plunger.” ECF No. 147 at 26-28.²⁸

3 Dependent claims 21 and 26 both recite a “linear actuator.” Dependent claim 21
4 recites: “The device of claim 20, wherein the barrier is configured to disestablish when
5 displaced by a **linear actuator**.” ’187 Patent col. 20 ll. 38-39 (emphasis added). Dependent
6 claim 26 recites: “The device of claim 24, wherein a **linear actuator** exerts the force on
7 the barrier.” *Id.* col. 20 ll. 51-52 (emphasis added).

8 DNA Genotek’s proposed construction for the term “linear actuator” is consistent
9 with descriptions in the claims and the specification of the components that perform the
10 disestablishing of the barrier. For example, dependent claim 24 recites: a device “wherein
11 engaging the thread on the sealing cap and the opening comprises exerting a force on the
12 barrier, wherein the force is perpendicular to a direction of rotation of the sealing cap.”
13 ’187 Patent col. 20 ll. 45-48. Additionally, when describing figures 10 and 11, the
14 specification explains:

15 As the cap is twisted on (shown [*sic*] by dotted line and arrow 10, ram 2, which
16 is attached to cap 1, moves downward as shown by dotted line arrow 11. This
17 downward movement forces plunger 4, which is contained in plunger barrel
18 5, downward as indicated by dotted line and arrow 12. The downward
19

20
21 at 38-39; ECF No. 74-2 at 22-23. As such, the Court rejects DNA Genotek’s waiver
22 argument.

23 ²⁸ In its responsive claim construction brief, Spectrum argues for the first time that the
24 term “linear actuator” should be construed as a § 112 ¶ 6 means-plus-function claim
25 element. ECF No. 88 at 10. The Court declines to address this new argument as it was not
26 presented in either the Parties’ Joint Claim Construction Chart or Spectrum’s Opening
27 Claim Construction Brief. *See* ECF No. 74-1 at 38-39; ECF No. 147 at 26-28; *see also*
28 *Bazuaye v. I.N.S.*, 79 F.3d 118, 120 (9th Cir. 1996) (“Issues raised for the first time in the
reply brief are waived.”); *Norman v. United States*, 429 F.3d 1081, 1091 (Fed. Cir. 2005)
 (“Arguments raised for the first time in a reply brief are not properly before this court.”
(citing *Novosteel SA v. U.S., Bethlehem Steel Corp.*, 284 F.3d 1261, 1274 (Fed. Cir.
2002))).

1 movement of plunger 4 forces sealing disc 7 to pivot, as shown by dotted line
 2 and arrow 13. Pivoting of disc 7 disestablishes the barrier between regions 8
 3 and 9, thereby permitting contact between the sample and a composition of
 4 the invention, shown as a dotted solution contained in region 9.

5 *Id.* at col. 15 ll. 39-49; *see also id.* figs. 10-11. In both of these examples, the component
 6 of the device that performs the disestablishing of the barrier is described as a component
 7 that converts rotational motion (*i.e.*, the twisting of the cap) into linear motion (*i.e.*,
 8 downward force perpendicular to the barrier). As such, DNA Genotek’s proposed
 9 construction is well supported by the intrinsic record.

10 In addition, DNA Genotek cites to persuasive extrinsic evidence. Specifically, a
 11 technical dictionary defining the term “linear actuator” as “a device that converts some
 12 kind of power into linear motion.” ECF No. Ex. 10, MCGRAW-HILL DICTIONARY OF
 13 ENGINEERING (5th ed. 1997). This definition of the term “linear actuator” is consistent with
 14 the descriptions in the intrinsic record of the components that perform the disestablishing
 15 of the barrier. As such, the Court adopts a slightly modified version of DNA Genotek’s
 16 proposed construction. The Court construes the claim term “linear actuator” as “a device
 17 that converts rotational motion into linear motion.”²⁹

18 Turning to Spectrum’s indefiniteness challenge, Spectrum’s contention that
 19 dependent claims 21 and 26 are invalid for failure to comply with 35 U.S.C. § 112 ¶ 4 and
 20 Spectrum’s alternative proposed construction both rest on the Court accepting Spectrum’s
 21 argument that independent claim 1 contains a means-plus-function claim element. *See* ECF
 22 No. 147 at 27-28. The Court has held that the claim term “when sealably closing said
 23

24
 25 ²⁹ The Court modifies DNA Genotek’s proposed construction to better match the ’187
 26 Patent’s descriptions of the components that perform the disestablishing of the barrier. The
 27 claims and the specification consistently describe the linear actuator embodiments as
 28 something that takes rotational motion and turns it into linear motion rather than the other
 way around. *See* ’187 Patent figs. 10-11, col. 15 ll. 39-49, col. 20 ll. 45-48.

opening with said sealing cap, the barrier mechanically disestablishes” is not a means-plus-function claim element. *See supra*. As such, the Court rejects Spectrum’s contention that dependent claims 21 and 26 are invalid for failure to comply with 35 U.S.C. § 112 ¶ 4, and rejects Spectrum’s alternative proposed construction for the claim term “linear actuator.”

G. “associates with”

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
The term does not require construction and should be accorded plain and ordinary meaning.	“contacts”	Plain and ordinary meaning.

Here, the Parties’ dispute whether the term “associates with” requires that the relevant components be in “contact” with each other. Spectrum argues that the term “associates with” requires contact between the relevant components. ECF No. 147 at 28. DNA Genotek argues that nothing in the intrinsic record of the ’187 Patent requires “associates with” to be redefined as “contacts.” ECF No. 134 at 21.

The Court begins its analysis of the Parties’ dispute by reviewing the claim language. The term “associates with” is found in dependent claim 34 of the ’187 Patent. Dependent claim 34 recites: “The device of claim 1, wherein the sealing cap associates with the containment vessel to create a fluid-tight seal.” ’187 Patent col. 21 ll. 7-9. The Court acknowledges that the language in claim 34 requires that the sealing cap and the containment vessel “associate[]” in a manner that creates “a fluid-tight seal.” *Id.* But as DNA Genotek correctly notes, this does not necessarily require physical contact between the sealing cap and the containment vessel as there could be an intermediate component between those two specific components that still allows for the creation of a fluid-tight seal. *See* ECF No. 134 at 21-22. Further, the common meaning of the word “associate” in

1 this context is “to join (things) together or connect (one thing) with another: COMBINE,”
2 which does not necessarily require physical contact. WEBSTER’S THIRD NEW
3 INTERNATIONAL DICTIONARY at 132 (1981); *see* MERRIAM-WEBSTER DICTIONARY,
4 <https://www.merriam-webster.com/dictionary/associate> (defining “associate” as “to join or
5 connect together: COMBINE”); *see also Phillips*, 415 F.3d at 1314 (explaining that the use
6 of general purposes dictionaries “may be helpful” in cases that involve “little more than
7 the application of the widely accepted meaning of commonly understood words”). For
8 example, two components could be connected or joined together by a third intermediate
9 component without the two components coming into physical contact with each other. As
10 such, the claim language is insufficient by itself to support adoption of Spectrum’s
11 proposed construction.

12 Turning to the specification, Spectrum argues that the specification supports its
13 proposed construction because the only examples in the specification displaying an
14 association between the cap and the containment vessel require contact between the two
15 components. ECF No. 147 at 28 (citing ’187 Patent figs 10-11). But “it is improper to read
16 limitations from a preferred embodiment described in the specification—even if it is the
17 only embodiment—into the claims absent a clear indication in the intrinsic record that the
18 patentee intended the claims to be so limited.” *Dealertrack*, 674 F.3d at 1327; *accord*
19 *Openwave*, 808 F.3d at 514. Here, there is no clear indication that Claim 34 should be
20 limited to the depiction in the two cited figures.

21 Finally, Spectrum argues that the Court should adopt its proposed construction
22 because the term “associates with” in the ’187 Patent should be construed consistently with
23 the term “associates with” in the ’646 Patent. ECF No. 147 at 28. In response, DNA
24 Genotek argues that Spectrum’s contention should be rejected because the specification of
25 an unrelated patent is not intrinsic evidence. ECF No. 89 at 13. The Court agrees with DNA
26 Genotek. Statements made in an unrelated patent are not relevant to claim construction.
27 *See Apple*, 757 F.3d at 1312 (“[S]tatements made in unrelated applications are not relevant
28 to claim construction.”); *see, e.g., Goldenberg v. Cytogen, Inc.*, 373 F.3d 1158, 1167–68

(Fed. Cir. 2004) (finding statements in another patent irrelevant to claim construction “[a]bsent a formal relationship or incorporation during prosecution” of the patent at issue). As such, the Court rejects Spectrum’s contention that the Court should rely on its arguments regarding the ’646 Patent to interpret a claim term in the ’187 Patent.

In sum, the Court rejects Spectrum’s proposed construction for this claim term. The Court gives the claim term “associates with” its plain and ordinary meaning, and the Court declines to construe the claim term.³⁰

³⁰ Spectrum argues that because the parties dispute the scope of this claim term, the Court must construe the claim term. ECF No. 88 at 1, 5, 14 (citing *O2 Micro*, 521 F.3d at 1361–62; *Eon*, 815 F.3d at 1318; *InfoGation Corp. v. Google LLC*, No. 21-CV-00843-H-LL, 2021 WL 5547072, at *5 (S.D. Cal. June 8, 2021)). Spectrum is incorrect and misunderstands the Federal Circuit’s holdings in *O2 Micro* and *Eon*. “When the parties present a fundamental dispute regarding the scope of a claim term, it is the court’s duty to resolve it.” *O2 Micro*, 521 F.3d at 1362; accord *InfoGation*, 2021 WL 5547072, at *5 (“If the parties dispute the scope of a certain claim term, it is the court’s duty to resolve the dispute.”). The Federal Circuit has explained that, in some instances, a determination that a claim term needs no construction or has plain and ordinary meaning may be inadequate, such as when the term’s ordinary meaning does not resolve the parties’ dispute. *See Eon*, 815 F.3d at 1318 (citing *O2 Micro*, 521 F.3d at 1361). But that is not the case here.

Here, the parties’ dispute with respect to this claim term is that Spectrum contends that the claim term “associates with” specifically requires that the components at issue be in contact with each other, and DNA Genotek disagrees and argues that the Court should reject this proposed requirement. By giving the claim term its plain and ordinary meaning, the Court has rejected Spectrum’s proposed requirement and thereby resolved the parties’ dispute with respect to the scope of this claim term in compliance with the Court’s duties under *Eon* and *O2 Micro*. *See, e.g., ActiveVideo Networks, Inc. v. Verizon Commc’ns, Inc.*, 694 F.3d 1312, 1326 (Fed. Cir. 2012) (finding district court did not violate the principles of *O2 Micro* by giving the claim terms their plain and ordinary meaning and rejecting a proposed construction that erroneously read limitations into the claims); *Summit 6*, 802 F.3d at 1291 (finding district court did not violate the principles of *O2 Micro* by giving claim term its plain and ordinary meaning); *Taction*, No. 3:21-cv-812-TWR-JLB, ECF No. 141 at 17 n.8 (“By giving the claim term its plain and ordinary meaning, the Court has rejected Apple’s proposed limitation and thereby resolved the parties’ dispute . . .”).

VI. CONSTRUCTION OF THE DISPUTED CLAIM TERMS FROM THE '646 PATENT

A. “biological sample”

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
The term does not require construction and should be accorded plain and ordinary meaning.	“cells”	“biological sample containing cells”

Here, the Parties dispute whether the claim term “biological sample” must be limited to “cells.” Spectrum argues that the '646 Patent makes clear that the claimed invention is directed to preserving cells. ECF No. 147 at 30-31. In response, DNA Genotek argues that Spectrum’s proposed construction seeks to impermissibly narrow the meaning of the claim term “biological sample” in a way that is not supported by the intrinsic record, and argues that the claim term instead should be given its plain and ordinary meaning. ECF No. 134 at 25.³¹

Independent claim 1 of the '646 Patent recites: “A kit for collecting and preserving a **biological sample**, the kit comprising . . . a sample collection reservoir having an opening configured to receive the **biological sample** from a user” '646 Patent col. 22 ll. 16-21

³¹ The term “biological sample” is contained inside the preamble of independent claim 1. *See* '646 Patent col. 22 ll. 16 (“A kit for collecting and preserving a biological sample”). In its briefing, DNA Genotek contends that the preamble of claim 1 is non-limiting and, therefore, the claim term “preserving a biological sample” is not a limitation because that term is contained within the preamble. *See* ECF No. 134 at 25-27. Although DNA Genotek contends that the broader claim term “preserving a biological sample” is not a limitation, DNA Genotek does not appear to contend that the narrower claim term “biological sample” is not a limitation because it is contained within the preamble. *Compare id. with id.* at 25-27.

(emphasis added). Turning to the specification, the Abstract of the '646 Patent states: "The disclosure relates to devices, solutions and methods for collecting and processing samples of bodily fluids containing cells . . . The tube is configured to receive a donor sample of bodily fluid (e.g., saliva, urine), which can then be subjected to processing to extract a plurality of cells." *Id.* at [57]; *see Hill–Rom Co., Inc. v. Kinetic Concepts, Inc.*, 209 F.3d 1337, 1341 n.* (Fed. Cir. 2000) (collecting cases) (explaining courts may "look[] to the abstract to determine the scope of the invention"). In addition, the specification states: "The disclosure relates to devices, solutions and methods for collecting samples of bodily fluids or other substances In addition, the disclosure relates generally to functional genomics and to the isolation and preservation of cells from such bodily fluids" '646 Patent col. 1 ll. 21-27; *see also id.* col. 6 ll. 47-48 ("this disclosure also relates to the isolation of cells from bodily fluids, such as saliva and urine, for these studies"), col. 17 ll. 34-36 ("The body fluids can contain a variety of cell types and the cells in the body fluids can be preserved by the solution according to the present disclosure."). In these passages, the specification explains that the invention disclosed in the '646 Patent specifically pertains to samples containing cells. As such, the Court will adopt a construction for this claim explaining that the claimed "biological sample" contains cells.

DNA Genotek argues that the specification distinguishes cells from other biological samples. ECF No. 134 at 25 (citing '646 Patent col. 6 ll. 46-49); ECF No. 89 at 14 (citing '646 Patent col. 6 ll. 46-53). The Court acknowledges that the specification does not equate the term "cells" with the term "samples," and, therefore, Spectrum's proposed construction is improper. Nevertheless, in the passages above and in the passage cited by DNA Genotek, the specification explains that the invention disclosed in the '646 Patent is specifically directed to samples containing cells. *See* '646 Patent at [57], col. 1 ll. 21-27, col. 6 ll. 46-53, col. 6 ll. 61-62.

In addition, DNA Genotek argues that a PHOSITA would understand that a biological sample would include more than just cells in the context of the '646 Patent. ECF No. 134 at 25; ECF No. 89 at 14. But a construction requiring the claimed "biological

sample” contain cells does not mean that the sample can only contain cells as opposed to other biological material. As such, DNA Genotek’s argument is misplaced.

In sum, the Court rejects both Parties’ proposed construction for the claim term “biological sample.” The Court construes “biological sample” as “biological sample containing cells.”

B. “preserving a biological sample”

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
The term does not require construction and should be accorded plain and ordinary meaning. If a construction is required, the Court should construe the term as “slowing degradation of a biological sample.”	“preventing cells from having their antigens degraded such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome”	“preventing cells in the biological sample from having their antigens degraded such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome”

Spectrum argues that within the context of the ’646 Patent, the claim “preserving a biological sample” specifically requires preserving the cells that make up the biological sample. ECF No. 147 at 29-31. In response, DNA Genotek argues that the term “preserving a biological sample” does not require construction because it only appears in the non-limiting preamble, and neither lexicography nor disavowal overturns the term’s plain and ordinary meaning. ECF No. 134 at 25-27.

The Court first addresses DNA Genotek’s contention that independent claim 1 of the ’646 Patent is non-limiting. Independent claim 1 of the ’647 patent contains the following preamble: “A kit for collecting and preserving a biological sample.” ’646 Patent col. 22 ll. 16.

1 “In general, a preamble limits the invention if it recites essential structure or steps,
2 or if it is ‘necessary to give life, meaning, and vitality’ to the claim.” *Catalina Mktg. Int’l,*
3 *Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (quoting *Pitney Bowes,*
4 *Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999)). “Conversely, a
5 preamble is not limiting ‘where a patentee defines a structurally complete invention in the
6 claim body and uses the preamble only to state a purpose or intended use for the
7 invention.’” *Id.* (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)); accord *Arctic*
8 *Cat Inc. v. GEP Power Prod., Inc.*, 919 F.3d 1320, 1328 (Fed. Cir. 2019). The Federal
9 Circuit has explained that “the rule against giving invention-defining effect to intended-
10 use preamble language reflects a longstanding substantive aspect of the patent statute—
11 specifically, the ‘well settled’ fundamental principle ‘that the recitation of a new intended
12 use for an old product does not make a claim to that old product patentable.’” *Arctic Cat*,
13 919 F.3d at 1328; see also *Catalina*, 289 F.3d at 809 (“[P]reambles describing the use of
14 an invention generally do not limit the claims because the patentability of apparatus or
15 composition claims depends on the claimed structure, not on the use or purpose of that
16 structure.”).

17 “Whether to treat a preamble as a limitation is a determination ‘resolved only on
18 review of the entire[] . . . patent to gain an understanding of what the inventors actually
19 invented and intended to encompass by the claim.’” *Catalina*, 289 F.3d at 808 (quoting
20 *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257 (Fed. Cir.
21 1989)). “No litmus test defines when a preamble limits claim scope,” but the Federal
22 Circuit has recognized certain “guideposts” for making that determination. *Id.*

23 One of those guideposts is that: “When limitations in the body of the claim rely upon
24 and derive antecedent basis from the preamble, then the preamble may act as a necessary
25 component of the claimed invention.” *Eaton Corp. v. Rockwell Int’l Corp.*, 323 F.3d 1332,
26 1339 (Fed. Cir. 2003); accord *Pacing*, 778 F.3d at 1024; see *Catalina*, 289 F.3d at 808
27 (“[D]ependence on a particular disputed preamble phrase for antecedent basis may limit
28 claim scope because it indicates a reliance on both the preamble and claim body to define

1 the claimed invention.”); *see also Bell Commc’ns Rsch., Inc. v. Vitalink Commc’ns Corp.*,
2 55 F.3d 615, 620 (Fed. Cir. 1995) (“[A] claim preamble has the import that the claim as a
3 whole suggests for it. In other words, when the claim drafter chooses to use both the
4 preamble and the body to define the subject matter of the claimed invention, the invention
5 so defined, and not some other, is the one the patent protects.”). This guidepost is present
6 here. The claim term “a biological sample” in the preamble of claim 1 provides the
7 antecedent basis for the claim term “the biological sample” found in the body of claim 1.
8 *See* ’646 Patent col. 22 ll. 20-22 (“a sample collection reservoir having an opening
9 configured to receive the biological sample from a user into the sample collection
10 reservoir”).

11 The Court acknowledges that the body of claim 1 only includes the specific term
12 “biological sample” and not the broader phrase “preserving a biological sample.” But the
13 Federal Circuit’s decision in *Bio-Rad Laboratories, Inc. v. 10X Genomics Inc.*, 967 F.3d
14 1353 (Fed. Cir. 2020), is instructive on this point. In *Bio-Rad*, the preamble at issue recited
15 “[a] method for conducting a reaction in plugs in a microfluidic system.” *Id.* at 1370. The
16 terms “reaction” and “microfluidic systems” in the preamble provided antecedent basis for
17 the use of those terms in the body of the claim. *Id.* In light of this, the Federal Circuit found
18 the entire preamble limiting. *See id.* at 1370–72. The Federal Circuit explained: “The
19 language relied upon for antecedent basis in the preamble at issue is intertwined with the
20 rest of the preamble.” *Id.* at 1371. Thus, “[t]he fact that the terms ‘reaction’ and
21 ‘microfluidic systems’ provide antecedent basis for these terms in the body of the claim is
22 a strong indication that the preamble acts ‘as a necessary component of the claimed
23 invention.’” *Id.* (quoting *Eaton*, 323 F.3d at 1339). Similarly, here, the term “biological
24 sample” is intertwined with the broader phrase “collecting and preserving a biological
25 sample” in the preamble. As such, under the Federal Circuit’s decision in *Bio-Rad*, the fact
26 that the term “biological sample” provides antecedent basis for that term in the body of the
27 claim “is a strong indication that the preamble acts ‘as a necessary component of the
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1 claimed invention.” *Id.* As such, the Court rejects DNA Genotek’s argument that the
 2 preamble in claim 1 of the ’646 Patent is non-limiting.

3 With that issue resolved, the Court turns to the proper construction of the claim term
 4 “preserving a biological sample.” Independent claim 1 of the ’646 Patent recites: “A kit for
 5 collecting and preserving a biological sample, the kit comprising” ’646 Patent col. 22
 6 ll. 16-17. The Court has construed the claim term a “biological sample” as a “biological
 7 sample containing cells.” *See supra.*

8 The Abstract of the ’646 Patent states:

9 The disclosure relates to devices, solutions and methods for collecting and
 10 processing samples of bodily fluids containing cells (as well as embodiments
 11 for the collection, and processing and/or analysis of other fluids including
 12 toxic and/or hazardous substances/fluids). In addition, the disclosure relates
 13 generally to function genomic studies and to the isolation and preservation of
 14 cells from saliva and other bodily fluids (*e.g.*, urine), for cellular analysis.

15 With respect to devices for collection of bodily fluids, some embodiments
 16 include two mating bodies, a cap and a tube (for example), where, in some
 17 embodiments, the cap includes a closed interior space for holding a sample
 18 preservative solution and mates with the tube to constitute the (closed) sample
 19 collection device. Upon mating, the preservation solution flows into the
 20 closed interior space to preserve cells in the bodily fluid. The tube is
 21 configured to receive a donor sample of bodily fluid (*e.g.*, saliva, urine), which
 22 can then be subjected to processing to extract a plurality of cells.

23 *Id.* at [57]; *see Hill–Rom*, 209 F.3d at 1341 n.* (explaining courts may “look[] to the
 24 abstract to determine the scope of the invention”).³² Similarly, the specification in a section
 25 entitled “Field of the Disclosure” explains:

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 28 ³² In its briefing, DNA Genotek cites to a portion of the specification stating: “The one
 or more fluids or materials contained in the interior space 20 in the cap 12 may assist in

1 The disclosure relates to devices, solutions and methods for collecting
 2 samples of bodily fluids or other substances, including hazardous and/or toxic
 3 substances, and in particular, a naturally expressed bodily fluid (e.g., saliva,
 4 urine). In addition, the disclosure relates generally to functional genomics and
 5 to the isolation and preservation of cells from such bodily fluids

6 '646 Patent col. 1 ll. 21-27; *see also id.* col. 4 ll. 53-56 (“Embodiments of the disclosure
 7 provide . . . solutions and methods for preserving cells of samples collected”), col. 4
 8 ll. 47-49 (“there is a need for new solutions and methods that will preserve the antigenicity
 9 and epigenome of cells in other bodily fluids, such as saliva”), col. 17 ll. 34-36 (“[T]he
 10 cells in the body fluids can be preserved by the solution according to the present
 11 disclosure.”).

12 In the above passages, the specification expressly states that the “disclosure” of the
 13 '646 Patent encompasses preserving cells within that sample. “When a patentee ‘describes
 14 the features of the ‘present invention’ as a whole,’ he implicitly alerts the reader that ‘this
 15 description limits the scope of the invention.” *Luminara*, 814 F.3d at 1353 (quoting
 16 *Regents of Univ. of Minnesota*, 717 F.3d at 936); *accord Pacing*, 778 F.3d at 1024; *see also*
 17 *Poly-Am.*, 839 F.3d at 1136 (“[A]n inventor may disavow claims lacking a particular
 18 feature when the specification describes “the present invention” as having that feature.”).
 19 The Court acknowledges that in the above quoted passages, the specification does not use
 20 the exact phrase “the present invention” or “the invention.” But the passages at issue use
 21 the similar phrases “the present disclosure” and “the disclosure.” '646 Patent at [57] (“The
 22 disclosure”), col. 1 ll. 21-27 (“The disclosure”); col. 17 ll. 34-36 (“the present
 23 disclosure”). Claim terms “ordinarily cannot be construed broader than the disclosure in
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25
 26 preserving the sample body fluids contained in the reservoir 40 of the tube 14 during at
 27 least storage and shipping.” '646 Patent col. 12 ll. 36-40. But the Abstract of the '646 Patent
 28 explains that the fluid referenced here – the fluid contained in the cap – is a “sample
 preservation fluid” and that fluid is used “to preserve cells in the bodily fluid.” *Id.* at [57].

the specification.” *Indacon*, 824 F.3d at 1357; *see also Gentry Gallery*, 134 F.3d at 1480 (“[C]laims may be no broader than the supporting disclosure, and therefore that a narrow disclosure will limit claim breadth.”). Thus, the specification’s use of the phrases “the present disclosure” and “the disclosure” alerts the reader that invention disclosed in the ’646 Patent is directed to the preservation of cells in samples. *See, e.g., Regents of Univ. of California v. Affymetrix, Inc.*, No. 17-CV-01394-H-NLS, 2018 WL 1466408, at *5 (S.D. Cal. Mar. 26, 2018) (finding that disclaimers in the specification limited the claim term “a sample” specifically to “biological material that is analyzed for a target polynucleotide”). Further, the specification never references any type of preservation other than the preservation of cells. As such, the Court agrees with Spectrum that within the context of the invention disclosed in the ’646 Patent, preservation of a biological sample specifically encompasses preserving cells within that biological sample. *See also, e.g., UltimatePointer, L.L.C. v. Nintendo Co.*, 816 F.3d 816, 823 (Fed. Cir. 2016) (limiting scope of claims based on “[t]he specification repeatedly emphasiz[ing] that the invention is directed to a direct-pointing system”); *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1338 (Fed. Cir. 2011) (limiting scope of claims where broad reading of claim language was “not supported by the specification”); *Tap Pharm. Prod., Inc. v. Owl Pharms., L.L.C.*, 419 F.3d 1346, 1353 (Fed. Cir. 2005) (limiting scope of claims where “all of the 31 examples in the specification describe[d] the use of particles” in a certain manner); *AquaTex Indus., Inc. v. Techniche Sols.*, 419 F.3d 1374, 1381–82 (Fed. Cir. 2005) (limiting scope of claims to synthetic fibers where the specification “describe[d] numerous examples of commercial grade fiberfill, all of which are comprised entirely of synthetic materials”); *Eon*, 815 F.3d at 1320–21 (“A party is . . . ‘not entitled to a claim construction divorced from the context of the written description and prosecution history.’” (quoting *Nystrom v. TREX Co., Inc.*, 424 F.3d 1136, 1144–45 (Fed. Cir. 2005))).

Moreover, the specification of the ’646 Patent provides an express definition for what is meant by preserving cells in a sample. The specification provides: “For purposes of the disclosure, ‘preserving cells’ means preventing the cells from having their antigens

1 degraded, such that they can be purified or enriched based on their antigens, and preventing
2 alterations in the cellular epigenome.” ’646 Patent col. 16 ll. 23-27. Spectrum’s proposed
3 construction aligns with this express definition in the specification, and, thus, is well
4 supported by the intrinsic record. *See Phillips*, 415 F.3d at 1316 (“[T]he specification may
5 reveal a special definition given to a claim term by the patentee In such cases, the
6 inventor’s lexicography governs.”); *Edwards Lifesciences*, 582 F.3d at 1329 (explaining
7 that a patentee acts as his own lexicographer when the patentee “‘clearly set[s] forth a
8 definition of the disputed claim term in either the specification or prosecution history”’);
9 *see, e.g., Biogen*, 976 F.3d at 1336.

10 In an effort to counter Spectrum’s proposed construction and support its own
11 proposed construction, DNA Genotek cites to patent applications filed by Spectrum that
12 contain the phrase “preserving a biological sample.” ECF No. 134 at 26-27 (citing Ex. 17,
13 Ex. 18). The Court rejects DNA Genotek’s reliance on these patent applications.
14 “[S]tatements made in unrelated applications are not relevant to claim construction.” *See*
15 *Apple*, 757 F.3d at 1312; *see also, e.g., Goldenberg*, 373 F.3d at 1167–68 (finding
16 statements in another patent irrelevant to claim construction “[a]bsent a formal relationship
17 or incorporation during prosecution” of the patent at issue).

18 In sum, the Court adopts a slightly modified version of Spectrum’s proposed
19 construction for this claim term. The Court construes “preserving a biological sample” as
20 “preventing cells in the biological sample from having their antigens degraded such that
21 they can be purified or enriched based on their antigens, and preventing alterations in the
22 cellular epigenome.”

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C. “annular valve”

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
“valve with two cylinders where the cylinders move relatively to open/close the valve”	“ring shaped valve”	“ring shaped valve”

Here, the Parties dispute whether the claimed “annular valve” must be ring-shaped. DNA Genotek contends that the claimed “annular valve” need only be a valve with two cylinders. ECF No. 134 at 22-23. Spectrum argues that the claimed “annular valve” must be ring-shaped in addition to being a valve with two cylinders (inner and outer). ECF No. 147 at 32-33.

The Court begins its analysis of the Parties’ dispute by reviewing the claim language. Independent claim 1 of the ’646 Patent recites a kit comprising, among other things: a movable **annular valve** configured to associate with the cap and with the opening of the sample collection reservoir, the movable **annular valve** comprising:

an inner cylinder in fluid-tight association with the cap and comprising a sidewall, the sidewall comprising a fluid vent; and
an outer cylinder in fluid-tight association with the inner cylinder and associated with the opening of the sample collection reservoir, the outer cylinder comprising an aperture defined by an interior sidewall of the outer cylinder,

’646 Patent col. 22 ll. 31-41 (emphasis added). In claim 1, the claim language uses the adjective “annular” to modify the word “valve.” As Spectrum correctly notes, the common meaning of the word “annular” is ring-shaped. *See* ECF No. 83-14, Ex. 13, THE NEW OXFORD AMERICAN DICTIONARY at 63 (2001) (defining “annular” as “ring-shaped”);

1 WEBSTER’S THIRD NEW INTERNATIONAL DICTIONARY at 88 (1981) (defining “annular” as
2 “of or relating to a ring: forming a ring: shaped like a ring”); THE AMERICAN HERITAGE
3 COLLEGE DICTIONARY at 55 (3d ed. 1997) (defining “annular” as “[s]haped like or forming
4 a ring”); MERRIAM-WEBSTER DICTIONARY, [https://www.merriam-webster.com/dictionary/](https://www.merriam-webster.com/dictionary/annular)
5 annular (defining “annular” as “of, relating to, or forming a ring”). As such, the claim
6 language supports Spectrum’s proposed construction.³³ See *Phillips*, 415 F.3d at 1314
7 (explaining that the use of general purposes dictionaries “may be helpful” in cases that
8 involve “little more than the application of the widely accepted meaning of commonly
9 understood words”).

10 DNA Genotek argues that the “the claims do not describe the term as ‘ring-shaped,’
11 let alone mention a ring shape at all.” ECF No. 134 at 23. The Court disagrees. By using
12 the word “annular,” which means “ring-shaped,” the claim language describes the claimed
13 “valve” as being ring-shaped.

14 In an effort to support its proposed construction, DNA Genotek notes that “Claim 1
15 describes the claimed ‘annular valve’ as ‘*comprising . . . an inner cylinder . . . and an outer*
16 *cylinder.*’” ECF No. 134 at 23 (emphasis in original). DNA Genotek argues that this
17 language shows that that the claimed “annular valve” is at least a valve with two cylinders.
18 *Id.* The Court acknowledges that this language requires that the claimed “annular valve”
19 be a valve with at least two cylinders. Indeed, the Parties do not dispute that the claimed
20 “annular valve” includes two cylinders. See ECF No. 147 at 32-33; ECF No. 134 at 23. But
21 under the claim language, the claimed “valve” must not only have two cylinders; it must
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23 ³³ DNA Genotek criticizes Spectrum’s proposed construction for relying on a general-
24 purpose dictionary to discern the meaning of the technical term “annular valve.” ECF No.
25 134 at 23-24. DNA Genotek notes that scientific dictionaries are preferable over non-
26 scientific dictionaries. *Id.* at 24. But DNA Genotek has failed to present the Court with any
27 evidence, intrinsic or extrinsic, showing that the term “annular valve” is a technical term.
28 In addition, DNA Genotek has not provided the Court with any dictionary, technical or
non-technical, or other evidence showing that the word “annular” can mean something
other than ring-shaped. As such, the Court rejects DNA Genotek’s argument.

1 also be “annular” (*i.e.*, ring-shaped). The Court agrees with Spectrum that DNA Genotek’s
2 proposed construction seeks to improperly read the word “annular” out of the claim
3 language. *See Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1257
4 (Fed. Cir. 2010) (“Claims must be ‘interpreted with an eye toward giving effect to all terms
5 in the claim.’”); *Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.*, 853 F.3d 1272, 1288 n.10
6 (Fed. Cir. 2017) (“It is highly disfavored to construe terms in a way that renders them void,
7 meaningless, or superfluous.”).

8 Turning to the specification, the specification further supports Spectrum’s proposed
9 construction by consistently using the word “annular” to describe something that is ring-
10 shaped. Indeed, the specification uses the words “annular” and “ring” interchangeably.
11 *Compare* ’646 Patent col. 9 ll. 21-28 (referring to the breakaway portion of the “tamper
12 evident” cap displayed in Figures 7A and 7B as “an annular member”); *with* col. 15 ll. 56-
13 62 (referring to the breakaway portion of the “tamper evident” cap displayed in Figures 7A
14 and 7B as “tamper evident feature 160 which may be comprised of a ring”); *see also*
15 *Edwards Lifesciences*, 582 F.3d at 1329 (“The interchangeable use of the two terms is akin
16 to a definition equating the two.”). The specification also refers to an “annular blocking
17 member,” which is displayed in Figures 3A-3C as being ring-shaped. *See id.* figs. 3A-3C,
18 col. 5 ll. 50-55, col. 8 ll. 49-61, col. 14 ll. 37-53. As such, Spectrum’s proposed construction
19 is well supported by the intrinsic evidence.

20 In sum, the Court adopts Spectrum’s proposed construction, and the Court rejects
21 DNA Genotek’s proposed construction. The Court construes the term “annular valve” as
22 “ring-shaped valve.”

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D. “associate with” and variations³⁴

DNA Genotek’s Proposed Construction	Spectrum’s Proposed Construction	Court’s Construction
The term does not require construction and should be accorded plain and ordinary meaning.	“contact”	Plain and ordinary meaning.

Here, the Parties again dispute whether the term “associate with” and variations of that term require that the relevant components be in “contact” with each other. Spectrum argues that the term “associates with” requires contact between the relevant components. ECF No. 147 at 33-34. DNA Genotek argues that nothing in the intrinsic record of the ’646 Patent requires “associates with” to be redefined as “contacts.” ECF No. 134 at 28.

The Court begins its analysis of the Parties’ dispute by reviewing the claim language. Independent claim 1 recites a kit comprising, among other things:

a movable annular valve configured to **associate with** the cap and with the opening of the sample collection reservoir, the movable annular valve comprising:

an inner cylinder in fluid-tight **association with** the cap and comprising a sidewall, the sidewall comprising a fluid vent; and

an outer cylinder in fluid-tight **association with** the inner cylinder and associated with the opening of the sample collection reservoir, the outer cylinder comprising an aperture defined by an interior sidewall of the outer cylinder

³⁴ The variations of the term “associate with” are “associated with,” “association with,” “association of,” and “configured to associate with.” ECF No. 147 at 33.

1 '646 Patent col. 22 ll. 31-41 (emphasis added). Here, there is nothing in the claim language
2 specifically requiring that the relevant components be in physical contact with each other.

3 Spectrum argues that the claim language supports its proposed construction. ECF
4 No. 88 at 15. Specifically, Spectrum contends that because the claim language already
5 recites that the claimed “outer cylinder” is part of the cap that is connected to the opening,
6 there is no reason to recite that the outer cylinder is “associated with” the opening unless
7 “associated with” means in physical contact with. *Id.* The Court disagrees with Spectrum’s
8 contention that a plain meaning construction would render this claim language
9 meaningless. The claim language explains that the claimed kit contains a moveable annular
10 valve that is configured to associate with the cap and the opening. *See* '646 Patent col. 22
11 ll. 31-32. The claim language further explains that the outer cylinder is a component of the
12 annular valve and the outer cylinder associates with the opening. *See id.* at col. 22 ll. 37-
13 38. In so doing, the claim language explains that it is this component of the annular valve
14 that specifically associates with the opening as opposed to a different component of the
15 valve, such as the inner cylinder. As such, a plain meaning construction would not render
16 that claim language meaningless or superfluous.

17 Spectrum also argues that “associate with” must mean contact because contact is
18 required for the invention to work. ECF No. 147 at 34. Specifically, Spectrum argues that
19 the outer cylinder must move to release the contents of the reagent compartment through
20 contact with the opening of the sample collection reservoir. *Id.* The Court does not find this
21 argument persuasive. The claim language states that the claimed “annular valve” is
22 “moveable,” but there is no language in claim 1 expressly stating that the outer cylinder
23 moves via direct contact with the opening. *See* '646 Patent col. 22 ll. 31-47.

24 Turning to the specification, Spectrum argues that the specification supports its
25 proposed construction because the specification reinforces that the components of the
26 claimed device be “associated” with each other via physical contact. ECF No. 147 at 34.
27 To support this contention, Spectrum cites to a portion of the specification discussing
28 Figures 3A-3C and explaining that securely coupling cap 12 onto tube 14 “caus[es] the

1 coupling features 48 of the annular blocking member 62 to engage the coupling member
2 50 of the tube 14.” ’646 Patent fig. 3A-3C, col. 14 ll. 61-65. But “it is improper to read
3 limitations from a preferred embodiment described in the specification—even if it is the
4 only embodiment—into the claims absent a clear indication in the intrinsic record that the
5 patentee intended the claims to be so limited.” *Dealertrack*, 674 F.3d at 1327; *accord*
6 *Openwave*, 808 F.3d at 514. Here, there is no clear indication that the claims should be
7 limited to the cited example. The specification describes Figures 3A-3C as merely
8 displaying “an embodiment of the sample collection device . . . according to some
9 embodiments of the present disclosure.” ’646 Patent col. 8 ll. 49-58. As such, the
10 specification does not support Spectrum’s proposed construction.

11 Turning to the prosecution history, Spectrum notes that DNA Genotek represented
12 to the PTO that claim 1 of the ’646 Patent draws support from Figures 3A and 3B in the
13 patent specification. ECF No. 147 at 33 (citing ECF No. 83-8, Ex. 7). But Spectrum fails
14 to adequately explain why this is of any consequence given that the specification of the
15 ’646 Patent explains that Figures 3A-3C merely represent embodiments of the claimed
16 sample collection device. Spectrum does not argue that these statements constitute
17 prosecution history disclaimer. As such, the Court rejects Spectrum’s reliance on the
18 prosecution history.

19 In sum, the Court rejects Spectrum’s proposed construction. The Court gives the
20 term “associate with” and the related terms their plain and ordinary meaning, and the Court
21 declines to construe the claim terms.

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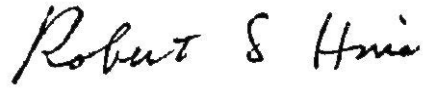
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1 **VII. CONCLUSION**

2 The Court construes the claims as stated in this Order.³⁵

3 **SO ORDERED.**

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5 Dated: November 29, 2022



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Hon. Robert S. Huie
United States District Judge

35 In addition, the Court denies as moot DNA Genotek's motion for leave to file a response to Spectrum's evidentiary objections.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

DNA GENOTEK INC., a California
Corporation,

Plaintiff,

v.

SPECTRUM SOLUTIONS L.L.C., a Utah
Limited Liability Company,

Defendant.

Case No.: 3:21-CV-00516-RSH-DDL

**ORDER GRANTING DEFENDANT’S
MOTION FOR SUMMARY
JUDGMENT OF NON-
INFRINGEMENT**

[ECF No. 231.]

On January 30, 2023, Defendant Spectrum Solutions L.L.C. (“Spectrum”) filed a motion for summary judgment of non-infringement of the asserted patents. ECF No. 231. On February 17, 2023, Plaintiff DNA Genotek Inc., (“Genotek”) filed a response in opposition to Spectrum’s motion for summary judgment. ECF No. 243. On February 27, 2023, Spectrum filed a reply. ECF No. 254. On February 27, 2023, the parties filed their joint statement of undisputed material facts. ECF No. 258.

The Court held a hearing on the matter on April 20, 2023. For the reasons below, the Court grants Spectrum’s motion for summary judgment.

I. BACKGROUND

Genotek is the owner by assignment of U.S. Patent Nos. 10,619,187 (“the ’187 Patent”) and 11,002,646 (“the ’646 Patent”) (collectively “the asserted patents”). *See* U.S. Patent No. 10,619,187, at [73] (issued Apr. 14, 2020); U.S. Patent No. 11,002,646, at [73] (issued May 11, 2021). In the present action, Genotek alleges that Spectrum infringes Claims 1, 2, 4, 6-7, 20-21, 23-31, and 33 of the ’187 Patent and Claims 1, 4-8, and 11-12 of the ’646 Patent. ECF No. 258 at 1 ¶¶ 2, 4 (listing the asserted claims). Specifically, Genotek alleges that Spectrum infringes the asserted claims, either literally or under the doctrine of equivalents, by making, using, offering for sale, selling and/or importing Spectrum’s SDNA-1000, SDNA-2000, and SDNA-3000 products (collectively “the accused products”). *See* SAC (Aug. 4, 2021), ECF No. 20 ¶¶ 3, 18, 22-27, 35-45, 55-65; ECF No. 258 at 1 ¶¶ 1, 2, 4.

The asserted patents both generally relate to devices for biological sample collection. The ’187 Patent was issued on April 14, 2020 and is entitled “Compositions and Methods for Obtaining Nucleic Acids from Sputum.” ’187 Patent at [54], [45]. The invention disclosed in the ’187 Patent “relates to compositions and methods for preserving nucleic acids at room temperature for extended periods of time and for simplifying the isolation of nucleic acids.” *Id.* col. 1 ll. 23-26. Specifically, the invention “features a composition for preserving nucleic acids that includes a chelating agent, and a denaturing agent, where the pH of the composition is greater than 5.0.” *Id.* col. 3 ll. 61-64.

Independent claim 1 of the ’187 Patent, the only independent claim in the ’187 Patent, claims:

1. A device for receiving and preserving nucleic acid in a biological sample, said device comprising:
 - a. one or more walls defining a containment vessel having a top having an opening, and a closed bottom having a sample receiving area for holding said biological sample, said opening for receiving a liquid sample and for sealably receiving a sealing cap, said top having an opening for receiving a biological

1 sample from the mouth of a user and further comprising at least one marking
2 on said one or more walls which corresponds to a fluid volume in the sample
3 receiving area;

4 b. a reagent compartment having a barrier, said barrier sealing and containing
5 reagents in said reagent compartment and capable of disestablishment to
6 release said reagents into the sample receiving area;

7 c. reagents in the reagent compartment for preserving nucleic acids potentially
8 present in the sample wherein said reagents comprise a denaturing agent, a
9 chelator and a buffer agent; and,

10 d. the sealing cap, whereby the device is configured such that, when sealably
11 closing said opening with said sealing cap, the barrier mechanically
12 disestablishes to release said reagents to form a mixture of reagents and said
13 biological sample wherein said buffering agent maintains a pH of said mixture
14 equal to or above 5.0 to preserve nucleic acids potentially present in the
15 sample.

16 '187 Patent col. 19 ll. 34-59.

17 The '646 Patent was issued on May 11, 2021 and is entitled "Devices, Solutions and
18 Methods for Sample Collection." '646 Patent at [54], [45]. The invention disclosed in the
19 '646 Patent generally relates to devices, solutions, and methods for collecting samples of
20 bodily fluids containing cells. *Id.* at [57], col. 1 ll. 21-24. The '646 Patent also generally
21 relates to the isolation and preservation of cells from such bodily fluids for cellular analysis.
22 *Id.* at [57], col. 1 ll. 24-29.

23 Independent claim 1 of the '646 Patent, the only independent claim in the '646
24 Patent, claims:

- 25 1. A kit for collecting and preserving a biological sample, the kit comprising:
26 a sample collection vessel, the sample collection vessel comprising:
27 a sample collection reservoir having an opening configured to receive
28 the biological sample from a user into the sample collection reservoir;

1 a connection member disposed on an exterior portion of the sample
2 collection vessel and adjacent to the opening;
3 a cap, the cap comprising:
4 a reagent chamber configured to store a reagent; and
5 a complementary connection member configured to engage the
6 connection member of the sample collection vessel; and
7 a movable annular valve configured to associate with the cap and with the
8 opening of the sample collection reservoir, the movable annular valve
9 comprising:
10 an inner cylinder in fluid-tight association with the cap and comprising
11 a sidewall, the sidewall comprising a fluid vent; and
12 an outer cylinder in fluid-tight association with the inner cylinder and
13 associated with the opening of the sample collection reservoir, the outer
14 cylinder comprising an aperture defined by an interior sidewall of the
15 outer cylinder,
16 wherein the aperture accommodates at least a portion of the inner
17 cylinder,
18 wherein the interior sidewall obstructs the fluid vent when the movable
19 annular valve is closed, and
20 wherein the interior sidewall does not obstruct the fluid vent when the
21 movable annular valve is open.

22 '646 Patent col. 22 ll. 16-47.

23 On March 24, 2021, Genotek filed a complaint for patent infringement against
24 Spectrum, alleging infringement of the '187 Patent. *See* Compl. (Mar. 24, 2021), ECF No.
25 1. On June 8, 2021, Genotek filed its Second Amended Complaint (the "SAC," the
26 operative complaint) against Spectrum, adding a claim for infringement of the '646 Patent.
27 *See* SAC (Aug. 4, 2021), ECF No. 20. On August 18, 2021, Spectrum filed an answer to
28 the SAC along with counterclaims against Genotek for: (1) declaratory judgment of non-

1 infringement of the asserted patents; (2) declaratory judgment of invalidity of the asserted
2 patents; (3) declaratory judgment of unenforceability of the '187 Patent due to inequitable
3 conduct; (4) monopolization in violation of section 2 of the Sherman Act, 15 U.S.C. § 2;
4 and (5) attempted monopolization in violation of section 2 of the Sherman Act, 15 U.S.C.
5 § 2. *See Answer & Counterclaims* (Aug. 18, 2021), ECF No. 27.

6 On September 2, 2021, the Court issued a scheduling order for the action. ECF No.
7 29. On April 1, 2022, the Court denied Genotek's motion to dismiss Spectrum's
8 counterclaims for inequitable conduct, monopolization, and attempted monopolization,
9 and the Court denied Genotek's motion to strike Spectrum's affirmative defenses of
10 inequitable conduct, patent misuse, and unclean hands. ECF No. 111. On May 25, 2022,
11 the Court issued an amended scheduling order. ECF No. 130.

12 On November 29, 2022, the Court issued a claim construction order construing the
13 agreed upon and disputed claim terms from the asserted patents. ECF No. 177. By the
14 present motion, Spectrum moves for summary judgment that the accused products do not
15 infringe either of the asserted patents. ECF No. 231-1 at 1-2, 18.

16 **II. LEGAL STANDARD FOR SUMMARY JUDGMENT**

17 Summary judgment is appropriate under Federal Rule of Civil Procedure 56 if the
18 moving party demonstrates "that there is no genuine dispute as to any material fact and the
19 movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *Celotex Corp. v.*
20 *Catrett*, 477 U.S. 317, 322 (1986). Material facts are facts that, under the governing
21 substantive law, may affect the outcome of the case. *Anderson v. Liberty Lobby, Inc.*, 477
22 U.S. 242, 248 (1986). A dispute as to a material fact is genuine if there is sufficient
23 evidence for a reasonable jury to return a verdict for the non-moving party. *Id.* "Disputes
24 over irrelevant or unnecessary facts will not preclude a grant of summary judgment." *T.W.*
25 *Elec. Serv., Inc. v. Pac. Elec. Contractors Ass'n*, 809 F.2d 626, 630 (9th Cir. 1987).

26 A party seeking summary judgment always bears the initial burden of demonstrating
27 that there is no genuine dispute as to any material fact. *Celotex*, 477 U.S. at 323. A moving
28 party without the ultimate burden of proof at trial can satisfy its burden in two ways: (1)

by presenting “evidence negating an essential element of the nonmoving party’s claim or defense;” or (2) by demonstrating “that the nonmoving party does not have enough evidence of an essential element to carry its ultimate burden of persuasion at trial.” *Nissan Fire & Marine Ins. Co. v. Fritz Companies, Inc.*, 210 F.3d 1099, 1102 (9th Cir. 2000). Once the moving party establishes the absence of a genuine dispute as to any material fact, the burden shifts to the nonmoving party to “set forth, by affidavit or as otherwise provided in Rule 56, ‘specific facts showing that there is a genuine issue for trial.’” *T.W. Elec. Serv.*, 809 F.2d at 630 (quoting former Fed. R. Civ. P. 56(e)); *accord Horphag Research Ltd. v. Garcia*, 475 F.3d 1029, 1035 (9th Cir. 2007). To carry this burden, the non-moving party “may not rest upon mere allegation or denials of his pleadings.” *Anderson*, 477 U.S. at 256; *see also Behrens v. Pelletier*, 516 U.S. 299, 309 (1996) (“On summary judgment, . . . the plaintiff can no longer rest on the pleadings.”). Rather, the nonmoving party “must present affirmative evidence . . . from which a jury might return a verdict in his favor.” *Anderson*, 477 U.S. at 256.

When ruling on a summary judgment motion, the court must view the facts and draw all reasonable inferences in the light most favorable to the non-moving party. *Scott v. Harris*, 550 U.S. 372, 378 (2007). The court should not weigh the evidence or make credibility determinations. *See Anderson*, 477 U.S. at 255. “The evidence of the non-movant is to be believed.” *Id.* Further, the court may consider other materials in the record not cited to by the parties, but it is not required to do so. *See Fed. R. Civ. P. 56(c)(3); see also Simmons v. Navajo Cnty.*, 609 F.3d 1011, 1017 (9th Cir. 2010) (“[A] district court has no independent duty ‘to scour the record in search of a genuine issue of triable fact.’”).

III. LEGAL STANDARD FOR PATENT INFRINGEMENT

A patent infringement analysis proceeds in two steps. *Niazi Licensing Corp. v. St. Jude Med. S.C., Inc.*, 30 F.4th 1339, 1350 (Fed. Cir. 2022); *JVW Enterprises, Inc. v. Interact Accessories, Inc.*, 424 F.3d 1324, 1329 (Fed. Cir. 2005). In the first step, the court construes the asserted claims as a matter of law. *See Niazi*, 30 F.4th at 1351; *JVW*, 424 F.3d at 1329. In the second step, the factfinder compares the properly construed claims to

1 the accused devices. *See id.*

2 ““The patentee bears the burden of proving infringement by a preponderance of the
3 evidence.”” *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1314 (Fed. Cir.
4 2011); *see Medtronic, Inc. v. Mirowski Fam. Ventures, LLC*, 571 U.S. 191, 193 (2014) (“A
5 patentee ordinarily bears the burden of proving infringement.”). “To prove infringement,
6 the plaintiff bears the burden of proof to show the presence of every element or its
7 equivalent in the accused device.” *Uniloc USA, Inc. v. Microsoft Corp.*, 632 F.3d 1292,
8 1301 (Fed. Cir. 2011); *accord Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364,
9 1378 (Fed. Cir. 2011). Under the doctrine of equivalents, “a product or process that does
10 not literally infringe . . . the express terms of a patent claim may nonetheless be found to
11 infringe if there is ‘equivalence’ between the elements of the accused product or process
12 and the claimed elements of the patented invention.” *Warner–Jenkinson Co. v. Hilton*
13 *Davis Chem. Co.*, 520 U.S. 17, 21 (1997); *accord Eagle Pharms. Inc. v. Slayback Pharma*
14 *LLC*, 958 F.3d 1171, 1175 (Fed. Cir. 2020).

15 The Federal Circuit “applies two articulations of the test for equivalence.” *Voda v.*
16 *Cordis Corp.*, 536 F.3d 1311, 1326 (Fed. Cir. 2008) (citing *Warner–Jenkinson*, 520 U.S.
17 at 21); *see UCB, Inc. v. Watson Lab’ys Inc.*, 927 F.3d 1272, 1284 (Fed. Cir. 2019). Under
18 the insubstantial differences test, “[a]n element in the accused device is equivalent to a
19 claim limitation if the only differences between the two are insubstantial.” *UCB*, 927 F.3d
20 at 1284 (quoting *Voda*, 536 F.3d at 1326). “Alternatively, under the function-way-result
21 test, an element in the accused device is equivalent to a claim limitation if it ‘performs
22 substantially the same function in substantially the same way to obtain substantially the
23 same result.’” *Voda*, 536 F.3d at 1326 (quoting *Schoell v. Regal Marine Indus., Inc.*, 247
24 F.3d 1202, 1209–10 (Fed. Cir. 2001)); *see Ajinomoto Co. v. Int’l Trade Comm’n*, 932 F.3d
25 1342, 1356 (Fed. Cir. 2019).¹ “Regardless how the equivalence test is articulated, ‘the

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27
28 ¹ The Federal Circuit has explained that “[t]he function-way-result test is particularly
suitable for analyzing the equivalence of mechanical devices.” *Crown Packaging Tech.*,

1 doctrine of equivalents must be applied to individual limitations of the claim, not to the
 2 invention as a whole.” *Mirror Worlds, LLC v. Apple Inc.*, 692 F.3d 1351, 1357 (Fed. Cir.
 3 2012) (quoting *Warner–Jenkinson*, 520 U.S. at 29).

4 “‘Infringement, whether literal or under the doctrine of equivalents, is a question of
 5 fact.’” *Advanced Steel Recovery, LLC v. X-Body Equip., Inc.*, 808 F.3d 1313, 1317 (Fed.
 6 Cir. 2015) (quoting *Absolute Software, Inc. v. Stealth Signal, Inc.*, 659 F.3d 1121, 1129–
 7 30 (Fed. Cir. 2011)). “Summary judgment of noninfringement is proper when no
 8 reasonable jury could find that every limitation recited in a properly construed claim is
 9 found in the accused device either literally or under the doctrine of equivalents.” *Id.*; see
 10 *EMD Millipore Corp. v. AllPure Techs., Inc.*, 768 F.3d 1196, 1201 (Fed. Cir. 2014).

11 **IV. LEGAL STANDARD FOR CLAIM CONSTRUCTION**

12 Because the first step in an infringement analysis is for the Court to construe the
 13 asserted claims as a matter of law, the Court sets forth the following legal standards
 14 governing claim construction. Claim construction is an issue of law for the court to decide.
 15 *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 326 (2015); *Markman v. Westview*
 16 *Instruments, Inc.*, 517 U.S. 370, 372 (1996). Although claim construction is ultimately a
 17 question of law, “subsidiary factfinding is sometimes necessary.” *Teva*, 574 U.S. at 326.

18 “It is a ‘bedrock principle’ of patent law that the ‘claims of a patent define the
 19 invention to which the patentee is entitled the right to exclude.’” *Phillips v. AWH Corp.*,
 20 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). “The purpose of claim construction is to
 21 ‘determin[e] the meaning and scope of the patent claims asserted to be infringed.’” *O2*
 22 *Micro Int’l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1360 (Fed. Cir. 2008).

23 Claim terms “are generally given their ordinary and customary meaning[,]” which
 24 “is the meaning that the term would have to a person of ordinary skill in the art
 25

26
 27 *Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009); see also *Warner–*
 28 *Jenkinson*, 520 U.S. at 39 (acknowledging that there is “substantial agreement” that the
 function-way-result test is “suitable for analyzing mechanical devices”).

1 [(“POSITA”)] in question at the time of the invention.” *Phillips*, 415 F.3d at 1312-13
 2 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). “In
 3 some cases, the ordinary meaning of claim language as understood by a [POSITA] may be
 4 readily apparent even to lay judges, and claim construction in such cases involves little
 5 more than the application of the widely accepted meaning of commonly understood
 6 words.” *Phillips*, 415 F.3d at 1314. “However, in many cases, the meaning of a claim term
 7 as understood by persons of skill in the art is not readily apparent.” *O2 Micro*, 521 F.3d at
 8 1360. If the meaning of the term is not readily apparent, the court must look to “those
 9 sources available to the public that show what a [POSITA] would have understood disputed
 10 claim language to mean.” *Phillips*, 415 F.3d at 1314 (quoting *Innova/Pure Water, Inc. v.*
 11 *Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). “Those sources
 12 include ‘the words of the claims themselves, the remainder of the specification, the
 13 prosecution history, and extrinsic evidence.’” *Phillips*, 415 F.3d at 1314 (quoting *Innova*,
 14 381 F.3d at 1116); see *Ericsson, Inc. v. D-Link Sys., Inc.*, 773 F.3d 1201, 1217-18 (Fed.
 15 Cir. 2014).

16 In determining the proper construction of a claim, a court should first look to the
 17 language of the claims. See *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1373 (Fed.
 18 Cir. 2019) (“[C]laim construction must begin with the words of the claims themselves.”);
 19 *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1299 (Fed. Cir. 2014) (“a
 20 claim construction analysis must begin and remain centered on the claim language itself”).
 21 The context in which a disputed term is used in the asserted claims may provide substantial
 22 guidance as to the meaning of the term. See *Phillips*, 415 F.3d at 1314.

23 A court must also read claims “in view of the specification, of which they are a part.”
 24 *Markman*, 52 F.3d at 979; see 35 U.S.C. § 112(b) (“The specification shall conclude with
 25 one or more claims particularly pointing out and distinctly claiming the subject matter
 26 which the inventor or a joint inventor regards as the invention.”). “Apart from the claim
 27 language itself, the specification is the single best guide to the meaning of a claim term.”
 28 *Vederi, LLC v. Google, Inc.*, 744 F.3d 1376, 1382 (Fed. Cir. 2014) (quoting *AIA Eng’g Ltd.*

1 v. *Magotteaux Int'l S/A*, 657 F.3d 1264, 1272 (Fed. Cir. 2011)). For example, “[a] claim
2 construction that excludes a preferred embodiment is rarely, if ever correct and would
3 require highly persuasive evidentiary support.” *Kaufman v. Microsoft Corp.*, 34 F.4th
4 1360, 1372 (Fed. Cir. 2022) (quoting *Epos Techs. Ltd. v. Pegasus Techs. Ltd.*, 766 F.3d
5 1338, 1347 (Fed. Cir. 2014)).

6 But “[t]he written description part of the specification does not delimit the right to
7 exclude. That is the function and purpose of claims.” *Markman v. Westview Instruments,*
8 *Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (en banc); accord *Arlington Indus., Inc. v.*
9 *Bridgeport Fittings, Inc.*, 632 F.3d 1246, 1256 (Fed. Cir. 2011). Therefore, “it is improper
10 to read limitations from a preferred embodiment described in the specification—even if it
11 is the only embodiment—into the claims absent a clear indication in the intrinsic record
12 that the patentee intended the claims to be so limited.” *Dealertrack, Inc. v. Huber*, 674 F.3d
13 1315, 1327 (Fed. Cir. 2012); accord *Openwave Sys., Inc. v. Apple Inc.*, 808 F.3d 509, 514
14 (Fed. Cir. 2015).

15 In addition to the claim language and the specification, the patent’s prosecution
16 history may be considered if it is in evidence. *Phillips*, 415 F.3d at 1317. The prosecution
17 history “consists of the complete record of the proceedings before the PTO and includes
18 the prior art cited during the examination of the patent.” *Id.* “Like the specification, the
19 prosecution history provides evidence of how the PTO and the inventor understood the
20 patent.” *Id.* “Yet because the prosecution history represents an ongoing negotiation
21 between the PTO and the applicant, rather than the final product of that negotiation, it often
22 lacks the clarity of the specification and thus is less useful for claim construction purposes.”
23 *Id.* In addition, a court should also consult the prosecution history “so that the court can
24 exclude any interpretation that was disclaimed during prosecution.” *Sorensen v. Int’l Trade*
25 *Comm’n*, 427 F.3d 1375, 1378 (Fed. Cir. 2005) (citing *Phillips*, 415 F.3d at 1317).

26 In most situations, analysis of the intrinsic evidence will resolve claim construction
27 disputes. See *Teva*, 574 U.S. at 331; *Vitronics*, 90 F.3d at 1583; see also *Seabed*
28 *Geosolutions (US) Inc. v. Magseis FF LLC*, 8 F.4th 1285, 1287 (Fed. Cir. 2021) (“If the

1 meaning of a claim term is clear from the intrinsic evidence, there is no reason to resort to
2 extrinsic evidence.”). However, “[w]here the intrinsic record is ambiguous, and when
3 necessary,” district courts may “rely on extrinsic evidence, which ‘consists of all evidence
4 external to the patent and prosecution history, including expert and inventor testimony,
5 dictionaries, and learned treatises.’” *Power Integrations, Inc. v. Fairchild Semiconductor*
6 *Int’l, Inc.*, 711 F.3d 1348, 1360 (Fed. Cir. 2013) (quoting *Phillips*, 415 F.3d at 1317). A
7 court must evaluate all extrinsic evidence in light of the intrinsic evidence. *Phillips*, 415
8 F.3d at 1319. “[E]xtrinsic evidence is to be used for the court’s understanding of the patent,
9 not for the purpose of varying or contradicting the terms of the claims.” *Genuine Enabling*
10 *Tech. LLC v. Nintendo Co.*, 29 F.4th 1365, 1373 (Fed. Cir. 2022) (quoting *Markman*, 52
11 F.3d at 981); *see Summit 6, LLC v. Samsung Elecs. Co.*, 802 F.3d 1283, 1290 (Fed. Cir.
12 2015) (“Extrinsic evidence may not be used ‘to contradict claim meaning that is
13 unambiguous in light of the intrinsic evidence.’”). In cases where subsidiary facts
14 contained in the extrinsic evidence “are in dispute, courts will need to make subsidiary
15 factual findings about that extrinsic evidence.” *Teva*, 574 U.S. at 332.

16 “[D]istrict courts are not (and should not be) required to construe every limitation
17 present in a patent’s asserted claims.” *O2 Micro*, 521 F.3d at 1362; *see Eon Corp. IP*
18 *Holdings v. Silver Spring Networks*, 815 F.3d 1314, 1318-19 (Fed. Cir. 2016) (“[O]nly
19 those terms need be construed that are in controversy, and only to the extent necessary to
20 resolve the controversy.”). In certain situations, it is appropriate for a court to determine
21 that a claim term needs no construction and its plain and ordinary meaning applies. *See id.*;
22 *Phillips*, 415 F.3d at 1314. But “[a] determination that a claim term ‘needs no construction’
23 or has the ‘plain and ordinary meaning’ may be inadequate when a term has more than one
24 ‘ordinary’ meaning or when reliance on a term’s ‘ordinary’ meaning does not resolve the
25 parties’ dispute.” *O2 Micro*, 521 F.3d at 1361. When the parties present a dispute regarding
26 the scope of a claim term, it is the court’s duty to resolve the dispute. *Id.* at 1362; *Eon*, 815
27 F.3d at 1318.

28 //

V. SPECTRUM'S MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT OF THE '187 PATENT

Spectrum moves for summary judgment that the accused products do not infringe the '187 Patent because the accused products' "reagent compartment" is in the "cap," not the "container." ECF No. 231-1 at 11-14. In response, Genotek argues that Spectrum's motion should be denied because there is at least a genuine dispute of material fact as to whether the accused products satisfy the "reagent compartment" limitation under either a literal infringement analysis or a doctrine of equivalents analysis. ECF No. 242 at 10-18.

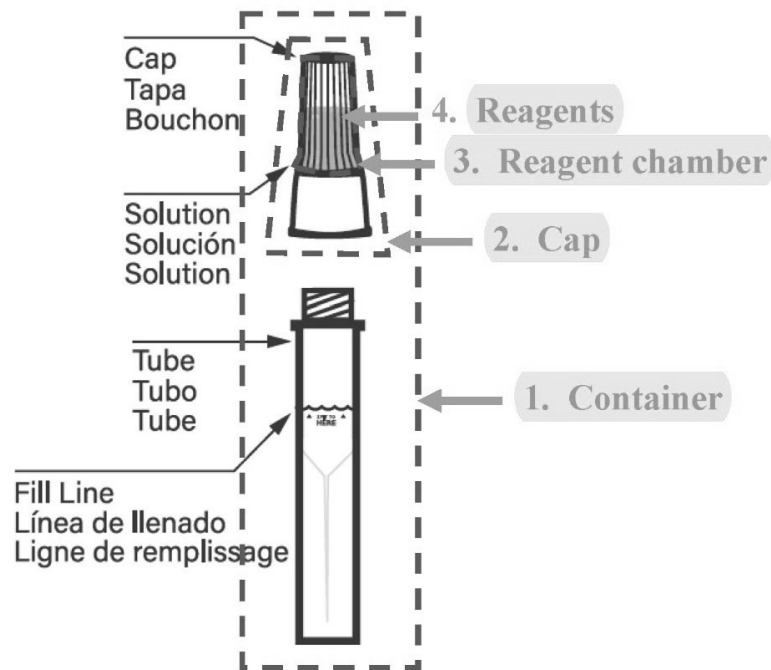
Independent claim 1 of the '187 Patent, the only independent claim in the '187 Patent, claims: "A device for receiving and preserving nucleic acid in a biological sample, said device comprising:" (1) "a containment vessel;" (2) "a sealing cap;" (3) "a reagent compartment;" and (4) "reagents." '187 Patent col. 19 ll. 34-59. In the Court's claim construction order, the Court construed the term "containment vessel" as "container," and the Court construed the term "reagent compartment" as "region or section of the containment vessel." ECF No. 177 at 23, 44.

A. Literal Infringement

Spectrum argues that the accused products do not literally infringe any claim of the '187 Patent because it is undisputed that the reagent compartment of the accused products is in the cap and not in the container, as required by the Court's claim construction of the term "reagent compartment." ECF No. 231-1 at 11. In response, Genotek argues that there is a genuine dispute of material fact as to whether the accused devices satisfy the "reagent compartment" limitation because "a 'sealing cap' is part of the 'container' in the patented invention." ECF No. 242 at 8, 10-11. On reply, Spectrum argues that Genotek's theory of infringement cannot be correct because the claim language requires that the container be separate from the cap. ECF No. 254 at 1-2. Spectrum notes that the claim language states that the containment vessel/container "has 'a top having an opening,'" and that opening is "for receiving a liquid sample" and for "sealably receiving a sealing cap." *Id.* at 2 (citing '187 Patent col. 19 ll. 34-40).

The parties agree that the accused products each include “a funnel, a cap, and a tube.” ECF No. 258 at 1 ¶ 6. The parties further agree that the accused products’ “cap” “includes a compartment containing a reagent solution.” *Id.* at 1 ¶ 7.

Genotek’s theory of infringement is based on its contention that the accused products’ cap and tube combined constitute the “container” (i.e., the claimed “containment vessel”). *See* ECF No. 242 at 8, 10-11; *see also* ECF No. 242-8, Wereley Expert Report ¶¶ 25, 46-57. Indeed, in a chart contained in both Genotek’s opposition and Genotek’s expert’s report, Genotek and its expert identify the following structure (via a dotted rectangle) as constituting the claimed container/containment vessel:



ECF No. 242 at 11; ECF No. 242-8, Wereley Expert Report ¶¶ 25, 73.

This theory of infringement fails because it is based on an untimely and flawed claim construction argument. Genotek’s theory of infringement is based on its contention that the claimed “sealing cap” is part of the claimed “containment vessel.” *See* ECF No. 242 at 8 (“a ‘sealing cap’ is part of the ‘container’ in the patented invention”); *see also* ECF No. 242-8, Wereley Expert Report ¶¶ 47-53, 92 (citing to the ’187 Patent’s specification and prosecution history and contending “the term ‘container’ in the context of the ’187 Patent

encompasses a cap and a tube”).² At claim construction, Genotek did not seek a construction of the claim term “containment vessel” explaining that the “sealing cap” is part of the “containment vessel.” Indeed, Genotek didn’t seek a construction of the claim term “containment vessel” at all. Rather, Genotek argued that the term “containment vessel” did not require construction and instead should be given its plain and ordinary meaning. ECF No. 134 at 15; ECF No. 89 at 6; ECF No. 74-1, Ex. A at 28. As such, Genotek waived its present claim construction argument regarding the proper scope of the term “containment vessel.”³ See *CliniComp Int’l, Inc. v. Cerner Corp.*, No. 17-cv-2479-GPC-DEB, 2022 WL 16985003, at *9 (S.D. Cal. Nov. 15, 2022) (“[G]enerally, a party

² In his expert report, Dr. Wereley relies on the ’187 Patent’s specification and prosecution history to support his opinion that “the term ‘container’ in the context of the ’187 Patent encompasses a cap and a tube.” ECF No. 242-8, Wereley Expert Report ¶¶ 47-53, 92. Courts have held that “[e]xpert testimony about the plain and ordinary meaning of claim terms supported by reference to specification and prosecution history would constitute impermissible claim construction.” *CAO Lighting, Inc. v. Gen. Elec. Co.*, No. CV 20-681-GBW, 2023 WL 1930354, at *7 (D. Del. Jan. 30, 2023) (quoting *Ferring Pharms. Inc. v. PAR Pharm., Inc.*, No. 1:15-CV-00173-RGA, 2016 WL 6471246, at *1 (D. Del. Oct. 28, 2016)); see *Optolum, Inc. v. Cree, Inc.*, No. 1:17CV687, 2021 WL 8533814, at *3 (M.D.N.C. Oct. 24, 2021); *Contour IP Holding, LLC v. GoPro, Inc.*, No. 3:17-CV-04738-WHO, 2020 WL 5106845, at *4 (N.D. Cal. Aug. 31, 2020); *Not Dead Yet Mfg., Inc. v. Pride Sols., LLC*, 222 F. Supp. 3d 657, 661–62 (N.D. Ill. 2016); *MediaTek inc. v. Freescale Semiconductor, Inc.*, No. 11-CV-5341 YGR, 2014 WL 971765, at *5 (N.D. Cal. Mar. 5, 2014). And those courts have excluded such testimony. See *id.*; see also, e.g., *Cordis Corp. v. Bos. Sci. Corp.*, 561 F.3d 1319, 1337 (Fed. Cir. 2009) (affirming district court’s refusal to permit defendant to argue the prosecution history of the asserted patent to the jury). As such, the Court strikes and excludes this claim construction analysis in Dr. Wereley’s expert report.

³ In concluding that Genotek waived this particular claim construction argument, the Court notes that it is clear from Genotek’s claim construction briefing that, during the claim construction phase of this case, Genotek was well aware of the non-infringement defense that is contained in the present motion for summary judgment. See ECF No. 134 at 15 (“As described in more detail below, this unusual construction [for the term ‘containment vessel’] is step one in Spectrum’s two-step manufacture of a non-infringement defense.”); see also ECF No. 74-1, Ex. A at 34.

1 waives any argument with respect to the construction of a claim term when they fail to
2 raise that issue during the claim construction phase of the case.”); *Finalrod IP, LLC v. John*
3 *Crane, Inc.*, No. 7:15-cv-97, 2019 WL 4061703, at *2 (W.D. Tex. May 30, 2019) (“The
4 Federal Circuit holds that an accused infringer waives any argument with respect to the
5 construction of a claim term when they fail to raise that issue during the claim construction
6 phase of a patent infringement action.”); *see, e.g., Cent. Admixture Pharmacy Servs., Inc.*
7 *v. Advanced Cardiac Sols., P.C.*, 482 F.3d 1347, 1356 (Fed. Cir. 2007) (“The district court
8 found that ACS waived any argument with respect to th[e] term [“maintaining”] by failing
9 to raise it during the claim construction phase. We agree.”); *Pelican Int’l, Inc. v. Hobie Cat*
10 *Co.*, No. 320CV02390RSHMSB, 2023 WL 2127994, at *8, 11 (S.D. Cal. Feb. 10, 2023).
11 “‘Sound practical reasons counsel against construing additional terms based on claim
12 construction arguments raised for the first time in summary judgment briefs.’” *CliniComp*,
13 2022 WL 16985003, at *9 (quoting *Apple, Inc. v. Samsung Elecs. Co.*, No. 12-cv-630, 2014
14 WL 252045, at *3 (N.D. Cal. Jan. 21, 2014)); *see O2 Micro Int’l Ltd. v. Monolithic Power*
15 *Sys., Inc.*, 467 F.3d 1355, 1364 (Fed. Cir. 2006) (explaining that patent local rules are
16 designed to “prevent the shifting sands approach to claim construction”). Because
17 Genotek’s theory of infringement relies on an untimely claim construction that it waived,
18 its current theory of infringement fails as a matter of law.

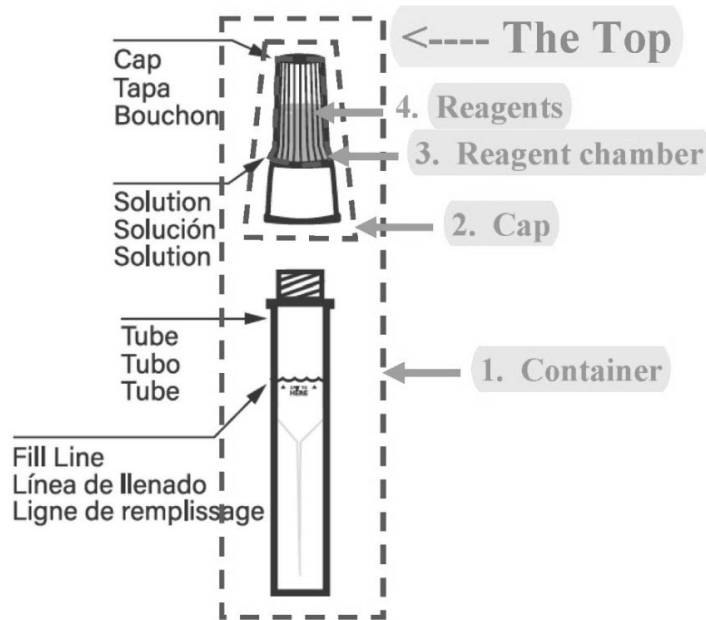
19 Further, Genotek’s claim construction argument is erroneous, and had Genotek
20 presented this argument to the Court during the claim construction phase of the case, the
21 Court would have rejected it. Genotek’s contention is that the claimed “sealing cap” is part
22 of the claimed “containment vessel.” *See* ECF No. 242 at 8 (“a ‘sealing cap’ is part of the
23 ‘container’ in the patented invention”); *see also* ECF No. 242-8, Wereley Expert Report ¶
24 92 (“the term ‘container’ in the context of the ’187 Patent encompasses a cap and a tube”).
25 The plain language of independent claim 1 of the ’187 claim makes clear that Genotek’s
26 contention is wrong. *See Phillips*, 415 F.3d at 1314 (explaining that “the context in which
27 a term is used in the asserted claim can be highly instructive”).
28

Independent claim 1 of the '187 Patent claims: "A device for receiving and preserving nucleic acid in a biological sample, said device comprising:" (1) "a containment vessel;" (2) "a sealing cap;" (3) "a reagent compartment;" and (4) "reagents." '187 Patent col. 19 ll. 34-59; *see also* ECF No. 176 at 16 (Genotek explaining: "I think of the claim as having three different sections. You've got the containment vessel[,] . . . then you've got the reagent compartment . . . [a]nd then you have the sealing cap."). "Where a claim lists elements separately, 'the clear implication of the claim language' is that those elements are 'distinct component[s]' of the patented invention." *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1254 (Fed. Cir. 2010) (quoting *Gaus v. Conair Corp.*, 363 F.3d 1284, 1288 (Fed. Cir. 2004)); *see Kyocera Senco Indus. Tools Inc. v. Int'l Trade Comm'n*, 22 F.4th 1369, 1382 (Fed. Cir. 2022) ("The asserted claims list th[e] elements separately There is, therefore, a presumption that those components are distinct."); *Echologics, LLC v. Orbis Intelligent Sys., Inc.*, No. 21-CV-01147-RBM-AHG, 2022 WL 2193115, at *10 (S.D. Cal. June 17, 2022). Because claim 1 lists "a containment vessel" and "a sealing cap" separately, there is a presumption that those two components are distinct.

Further, the claim language in independent claim 1 provides that the "containment vessel" has "a top having an opening . . . said opening for receiving a liquid sample and for sealably receiving a cap." '187 Patent col. 19 ll. 36-40. The plain and ordinary meaning of the word "top" is "[t]he uppermost part, point, surface, or end." THE AMERICAN HERITAGE COLLEGE DICTIONARY 1426 (3d ed. 1997); *see* MERRIAM-WEBSTER DICTIONARY, <https://www.merriam-webster.com/dictionary/top> (defining "top" as "the highest point, level, or part of something.").⁴ If the cap is part of the containment vessel, then the

⁴ At the hearing, Genotek conceded that the common definition of the word "top" is "uppermost part," but it argued that the term "top" is context-specific in this situation. ECF No. 312 at 7. At claim construction, Genotek did not propose that the Court construe the term "top." *See generally* ECF No. 74-1, Ex. A; ECF No. 134; ECF No. 89. As such, Genotek has waived any argument that the claim term "top" means anything other than the

containment vessel does not have a top with an opening because the uppermost part or point of the containment vessel would be the top of the cap, which is enclosed and does not have an opening for receiving a cap. This can be displayed via Genotek's own diagram in its opposition brief:



ECF No. 242 at 11 (annotated by Court). The uppermost part/point, or “top,” of what Genotek identifies as the “Container” in its diagram is the top of the cap, which is enclosed and doesn’t have an opening (in particular, it doesn’t have an opening for receiving a cap).

At the hearing, Genotek contended that although it is not a method claim, the claim language in independent claim 1 contemplates steps or stages where the container changes over time. *See* ECF No. 312 at 4-6, 8; *see also* ECF No. 242 at 10 (“[O]nce the cap is placed on the collection tube as intended, the cap and the collection tube form the required ‘container.’”). The Court rejects this argument. Even if the Court were to assume that Genotek’s contention that the apparatus described in claim 1 recites steps or stages is

plain and ordinary meaning of the word “top,” which is “uppermost part.” *See Cent. Admixture Pharmacy*, 482 F.3d at 1356; *CliniComp*, 2022 WL 16985003, at *9; *Pelican*, 2023 WL 2127994, at *8, 11; *Finalrod*, 2019 WL 4061703, at *2.

1 correct, as Genotek acknowledged at the hearing, the term “top” and the term “containment
2 vessel” are only recited in what Genotek described as “step (a)” of the claim. ECF No. 312
3 at 5. As such, there is no support in the claim language for Genotek’s contention that the
4 containment vessel or the top of that containment vessel changes over time.

5 In an effort to support its claim construction position, Genotek also cites figures 10
6 and 11 in the specification and the corresponding descriptions of those figures. ECF No.
7 242 at 16. Genotek contends that the specification “describes Figures 10 and 11 as being
8 views of the ‘container,’ views that include ‘cap 1.’ *Id.* The Court rejects Genotek’s
9 contention. Figures 10 and 11 are views of the “container,” but the corresponding
10 descriptions in the specification specifically state that the “container” in those figures is
11 “container 3,” and figures 10 and 11 depict “container 3” as being a separate component
12 apart from and below “cap 1.” *See* ’187 Patent figs 10, 11, col. 8 ll. 46-54, col. 15 ll. 33-
13 39. As such, figures 10 and 11 are consistent with the notion that the “containment vessel”
14 and the “sealing cap” are separate components of the device.⁵

15
16
17 ⁵ Genotek also cites the specification’s description of the “desirable features” of the
18 “collection vessel” / “collection device of the invention.” ECF No. 242 at 15 (citing ’187
19 Patent col. 14 ll. 61-67, col. 15 ll. 1-32). DNA Genotek’s citation of this passage is based
20 on its assumption that the specification equates the terms “collection device of the
21 invention” and “collection vessel” with the term “container.” But it is unclear from the
22 specification that this is a correct assumption. *See, e.g.,* ’187 Patent col. 6 ll. 28-33 (“The
23 device: includes a container, . . . a means for closing the container,”); *id.* at col. 14 ll.
24 51-56 (same). Further, even if Genotek is correct, and the specification equates these terms,
25 there is other language in the specification describing the “cap” as not only being separate
26 from the “container,” but also as being separate from “the device.” *See, e.g., id.* at col. 15
27 ll. 34-35 (“[w]ith cap 1 not attached to the device, a biological sample (not shown) is
28 applied to a first region 8 of container 3”), (“cap 1 is placed onto the device and secured
via a screw thread mechanism to a tight fit, thereby sealing container 3”). Moreover,
regardless of any ambiguous language contained in the specification, as explained above,
the claim language itself clearly states that the claimed “containment vessel” has “a top”
with “an opening” “for sealably receiving a sealing cap,” mandating that the cap be a
separate component from the containment vessel. ’187 Patent col. 19 ll. 36-40.

1 Genotek also cites to extrinsic evidence consisting of an unrelated patent – U.S.
2 Patent No. 5,643,767 – and testimony from Spectrum’s experts discussing that unrelated
3 patent. *See* ECF No. 242 at 11-12 (citing ECF No. 243-11, Fischetti Decl. ¶ 10; ECF No.
4 243-12, Ex. 12; ECF No. 243-13, Leinsing Expert Report ¶¶ 50-63). But this evidence is
5 of no consequence because statements from or regarding an unrelated patent are irrelevant
6 for claim construction purposes. *See Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1312
7 (Fed. Cir. 2014) (“statements made in unrelated applications are not relevant to claim
8 construction”); *Taction Tech., Inc. v. Apple Inc.*, No. 21-CV-812 TWR (JLB), 2022 WL
9 18781398, at *15 (S.D. Cal. Sept. 28, 2022) (“[T]he two cited Apple patents are unrelated
10 to the patents-in-suit, and, thus are not relevant to claim construction.”); *see also, e.g.*,
11 *Goldenberg v. Cytogen, Inc.*, 373 F.3d 1158, 1167–68 (Fed. Cir. 2004) (finding statements
12 in another patent irrelevant to claim construction “[a]bsent a formal relationship or
13 incorporation during prosecution” of the patent at issue).

14 Finally, in its claim construction briefing, Genotek contended that something that is
15 in the cap is “outside of the containment vessel,” demonstrating Genotek recognized that
16 the containment vessel is a separate component from the cap. *See, e.g.*, ECF No. 134 at 17
17 (“The specification of Provisional Application No. 60/386,398 (‘398 application’)—
18 whose content the ’187 patent incorporates expressly by reference—even discloses an
19 embodiment in which *the reagent compartment is outside of the containment vessel*, e.g.,
20 as part of the cap.” (emphasis in original)). In sum, Genotek’s claim construction argument
21 is erroneous and contrary to the language in the claims, and, therefore, the Court rejects it.

22 And for the same reasons, the relevant claim language makes it clear that summary
23 judgment of no literal infringement is appropriate here. No reasonable jury could look at
24 the diagram from Genotek and its expert and conclude that the top of the structure identified
25 by Genotek has an opening for receiving a cap. Any person viewing the diagram would see
26 that the uppermost part/point of the structure identified by Genotek and its expert as being
27
28

the “container” is the top of the cap.⁶ See ECF No. 242 at 11; ECF No. 242-8, Wereley Expert Report ¶¶ 25, 73. As such, no reasonable jury could conclude that the accused products literally satisfy the “containment vessel having a top having an opening . . . said opening for receiving a liquid sample and for sealably receiving a cap” claim limitation based on the structure identified by Genotek.⁷ Accordingly, Spectrum is entitled to summary judgment that the accused products do not literally infringe claim 1 of ’187 Patent. See *Advanced Steel Recovery*, 808 F.3d at 1317; *EMD Millipore*, 768 F.3d at 1201.

B. Doctrine of Equivalents

Genotek argues that even if there is no literal infringement, the Court should deny Spectrum’s motion for summary judgment because it has presented evidence that there is infringement under the doctrine of equivalents. ECF No. 242 at 15-18. In response, Spectrum argues that Genotek waived any reliance on infringement under the doctrine of

⁶ At the hearing, Genotek asserted that the structure identified in the diagram as the “Container” has an opening at the top of what is identified as the “tube,” and that constitutes the “top” of the containment vessel. ECF No. 312 at 4, 8; see ECF No. 242 at 11. But as Genotek conceded at the hearing, that opening is “halfway down” the diagram and near the middle of the structure identified by Genotek, and not at the top. See ECF No. 312 at 5 (Court: “So in step (a), the top is halfway down the drawing, just above where the word ‘tube’ exists on the drawing?” Genotek: “Yes. That’s right.”).

⁷ In the parties’ joint statement of undisputed material facts, the parties state: “For purposes of this motion, Spectrum does not dispute that the accused device meets the limitation of the asserted claims of the ’187 patent . . . other than the ‘reagent compartment’ [limitation].” ECF No. 258 at 1-2 ¶ 12. However, at the hearing, Spectrum clarified that its concession that the accused products satisfy the “containment vessel” limitation is based on Spectrum’s contention that the tube by itself (and only the tube) is the claimed “containment vessel.” ECF No. 312 at 12. Genotek declined to accept that concession from Spectrum, and, instead, Genotek contends that the tube and cap combined are the “containment vessel.” See ECF No. 242 at 8, 10-11. Genotek concedes that the claimed “reagent compartment” is in the “cap,” and the diagram contained in Genotek’s opposition brief displays the “reagent compartment” as being in the “cap” and not in what is identified as the “tube.” See *id.* at 11; ECF No. 231-5, Ex. 3 (“The reagent chamber is in the SDNA-1000’s cap.”); ECF No. 258 at 1 ¶ 7.

equivalents because Genotek never properly asserted doctrine of equivalents theories in its infringement contentions. ECF No. 231-1 at 11-13; ECF No. 254 at 5 n.4. The Court agrees with Spectrum.

“The Court’s Patent Local Rules are designed to require parties to crystallize their theories of the case early in the litigation and to adhere to those theories once they have been disclosed.” *CliniComp*, 2022 WL 16985003, at *12 (quoting *Wi-LAN Inc. v. LG Elecs., Inc.*, No. 18-CV-01577-H-BGS, 2019 WL 5790999, at *2 (S.D. Cal. Sept. 18, 2019)); accord *O2 Micro*, 467 F.3d at 1366 n.12. “The Local Rules are also designed to provide structure to discovery and to enable the parties to move efficiently toward claim construction and the eventual resolution of their dispute.” *Bell Semiconductor, LLC v. NXP USA, Inc.*, No. 22-CV-00594-H-KSC, 2023 WL 2342037, at *2 (S.D. Cal. Feb. 27, 2023) (quoting *Pelican Int’l, Inc. v. Hobie Cat Co.*, No. 320CV02390RSHMSB, 2023 WL 2127995, at *2 (S.D. Cal. Feb. 10, 2023)). “The Patent Local Rules accomplish this ‘by requiring both the plaintiff and the defendant in patent cases to provide early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those contentions when new information comes to light in the course of discovery. The Local Rules thus seek to balance the right to develop new information in discovery with the need for certainty as to the legal theories.’” *Id.* (quoting *O2 Micro*, 467 F.3d at 1365-66). “A district court has wide discretion in enforcing the Patent Local Rules.” *Echologics, LLC v. Orbis Intelligent Sys., Inc.*, No. 21-CV-01147-RBM-AHG, 2022 WL 17724142, at *7 (S.D. Cal. Dec. 15, 2022) (quoting *CliniComp*, 2022 WL 16985003, at *12); see *Howmedica Osteonics Corp. v. Zimmer, Inc.*, 822 F.3d 1312, 1320 (Fed. Cir. 2016) (reviewing “a district court’s application of its local rules for abuse of discretion”); see also *Mortg. Grader, Inc. v. First Choice Loan Servs. Inc.*, 811 F.3d 1314, 1321 (Fed. Cir. 2016) (“[T]his court defers to the district court when interpreting and enforcing local rules so as not to frustrate local attempts to manage patent cases according to prescribed guidelines.”).

“Under Patent Local Rule 3.1, a party claiming patent infringement must serve on

all parties a ‘Disclosure of Asserted Claims and Infringement Contentions,’ and those contentions must disclose specific information regarding the party’s theories of infringement in the case.” *Bell Semiconductor*, 2023 WL 2342037, at *2 (citing Patent L.R. 3.1). In a lawsuit for patent infringement in the Southern District of California, a patentee is limited to the infringement theories and the accused products it sets forth in its infringement contentions. *Id.*; *CliniComp*, 2022 WL 16985003, at *13; *see also LookSmart Grp., Inc. v. Microsoft Corp.*, No. 17-CV-04709-JST, 2019 WL 7753444, at *2 (N.D. Cal. Oct. 17, 2019) (“Once served, the infringement contentions constitute the universe of infringement theories.”). Any infringement theories not properly disclosed pursuant to the Court’s Patent Local Rules are barred from presentation at trial (whether through expert opinion testimony or otherwise). *Bell Semiconductor*, 2023 WL 2342037, at *3 (citing *Pelican*, 2023 WL 2127995, at *3). Indeed, the Federal Circuit has held that a party asserting a claim of infringement waives its right to raise infringement under the doctrine of equivalents by failing to timely disclose it in its infringement contentions. *See, e.g., Teashot LLC v. Green Mountain Coffee Roasters, Inc.*, 595 F. App’x 983, 987-88 (Fed. Cir. 2015) (affirming district court’s holding that plaintiff waived its right to raise infringement under the doctrine of equivalents by failing to timely disclose it as an infringement theory its infringement contentions); *see also CliniComp*, 2022 WL 16985003, at *13 (“[Plaintiff] waived its right to raise doctrine of equivalents by failing to properly disclose that theory of infringement in its infringement contentions.”); *PersonalWeb Techs. LLC v. Int’l Bus. Machines Corp.*, No. 16-CV-01266-EJD, 2017 WL 2180980, at *16 (N.D. Cal. May 18, 2017) (“Courts in this district have cited deficient infringement contentions as additional bases for granting summary judgment of noninfringement with respect to doctrine of equivalents.”).

Patent Local Rule 3.1(e) provides that a party’s “Disclosure of Asserted Claims and Infringement Contentions” must contain the following information, among other things: “[w]hether each element of each asserted claim is claimed to be literally present and/or present under the doctrine of equivalents in the Accused Instrumentality.” S.D. Cal. Pat.

1 L.R. 3.1(e). Courts in this district have held that a general reservation of the right to assert
 2 infringement under the doctrine of equivalents does not satisfy a plaintiff’s obligation to
 3 disclose its infringement analysis as required by Patent Local Rule 3.1(e). *Bell*
 4 *Semiconductor*, 2023 WL 2342037, at *7; *CliniComp*, 2022 WL 16985003, at *13; *Sonix*
 5 *Tech. Co. v. Yoshida*, No. 12CV380-CAB (DHB), 2014 WL 11899474, at *3 (S.D. Cal.
 6 Dec. 12, 2014); *see also Finjan, Inc. v. Proofpoint, Inc.*, No. 13-CV-05808-HSG, 2015 WL
 7 9460295, at *1 (N.D. Cal. Dec. 23, 2015) (“Such a general disclaimer would be contrary
 8 to the local rule’s requirement that parties crystallize their theories early in the litigation.”).
 9 “Rather, in order to properly assert an infringement theory under the doctrine of equivalents
 10 in compliance with the Court’s Patent Local Rules, a patentee must provide ‘a limitation-
 11 by-limitation’ analysis as to why and how there is infringement under the doctrine of
 12 equivalents.” *Bell Semiconductor*, 2023 WL 2342037, at *7 (quoting *Pelican*, 2023 WL
 13 2127995, at *5); *CliniComp*, 2022 WL 16985003, at *13 (citing *Ameranth, Inc. v. Pizza*
 14 *Hut, Inc.*, No. 12CV1627 JLS NLS, 2013 WL 3894880, at *5 (S.D. Cal. July 26, 2013));
 15 *see also Mirror Worlds*, 692 F.3d at 1357 (“[T]he doctrine of equivalents must be applied
 16 to individual limitations of the claim, not to the invention as a whole.”). The infringement
 17 contentions must explain how there is infringement under the insubstantial differences test
 18 and/or the function-way-results test. *See ASUS Comput. Int’l v. Round Rock Rsch., LLC*,
 19 No. 12-CV-02099, 2014 WL 1463609, at *3 (N.D. Cal. Apr. 11, 2014) (“[I]n infringement
 20 contentions, ‘a party looking to rely on equivalents still has to describe how [the
 21 function/way/result or insubstantial differences] requirements are met.’”); *see, e.g., Bell*
 22 *Semiconductor*, 2023 WL 2342037, at *7 (finding contentions sufficient where they
 23 “analyze[d] equivalence on a limitation-by-limitation basis and provide specific analysis
 24 under the insubstantial differences test and the function-way-results test”); *Pelican*, 2023
 25 WL 2127995, at *6 (same).

26 Following the Court’s issuance of the claim construction order on November 29,
 27 2022, Genotek served its amended infringement contentions on December 29, 2022. *See*
 28 ECF No. 231-5, Ex. 3. In those contentions, for several claim limitations, including the

1 “reagent compartment” claim limitation, Genotek states:

2 To the extent this claim limitation is not literally met, the SDNA-1000 meets
3 that limitation under the doctrine of equivalents because any differences are
4 insubstantial and the SDNA-1000 performs substantially the same function in
5 substantially the same way to get substantially the same result.

6 *See, e.g., id.* at 113, 116, 119, 122.

7 This is a general reservation of right to assert infringement under the doctrine of
8 equivalents and is insufficient to comply with Patent Local Rule 3.1(e). The Court
9 acknowledges that this reservation of right is done on a limitation-by-limitation basis and
10 references the insubstantial differences test and the function-way-results tests. But simply
11 saying the words “insubstantial” and “function”-“way”-“result” is insufficient to comply
12 with Rule 3.1(e). Rather, the patentee must provide some analysis explaining “why and
13 how” there is infringement under the insubstantial differences test and/or the function-way-
14 results test.⁸ *See Bell Semiconductor*, 2023 WL 2342037, at *7; *CliniComp*, 2022 WL

15
16
17 ⁸ The Court notes that this is not an onerous burden and can generally be satisfied with
18 just a few sentences of analysis. *See, e.g., Bell Semiconductor*, 2023 WL 2342037, at *7;
19 *Pelican*, 2023 WL 2127995, at *6. Indeed, in his expert report, Genotek’s expert Dr.
20 Wereley sets forth a theory of infringement under the doctrine of equivalents utilizing the
21 function-way-results test as to the “reagent compartment” limitation in five short sentences.
22 *See* ECF No. 242-8, Wereley Expert Report ¶ 93.

23 In its opposition, Genotek contends that if Spectrum had a complaint about its ability
24 to understand Genotek’s doctrine of equivalents theory of infringement, then it should have
25 raised the issue as a discovery dispute. ECF No. 242 at 17. The Court rejects Genotek’s
26 attempt to shift the responsibility of its infringement disclosures to Spectrum. Under the
27 plain language of Patent Local Rule 3.1, it is the responsibility of the “party claiming patent
28 infringement” (here, Genotek) to provide the information required by Rule 3.1(e). Pat. L.R.
3.1; *see KlausTech, Inc. v. Google LLC*, No. 10CV05899JSWDMR, 2018 WL 5109383, at
*6 (N.D. Cal. Sept. 14, 2018) (“KlausTech attempts to shift the blame to Google for not
complaining earlier about the inadequacy of its accused browser disclosures. This
argument is contrary to the patent local rules which place the burden on the patentee to
make explicit disclosures regarding all infringement theories.”); *Polaris PowerLED*

16985003, at *13; *Ameranth*, 2013 WL 3894880, at *5; *ASUS*, 2014 WL 1463609, at *3. As such, because Genotek failed to properly disclose any theory of infringement under the doctrine of equivalents in its infringement contentions, Genotek waived its right to raise infringement under the doctrine of equivalents.⁹ See, e.g., *Teashot*, 595 F. App'x at 987-88; *CliniComp*, 2022 WL 16985003, at *13; *Sonix*, 2014 WL 11899474, at *3.

Further, even if the Court were to assume that Genotek did not waive infringement under the doctrine of equivalents, summary judgment of non-infringement as to claim 1 of the '187 Patent is still appropriate. “[T]he doctrine of equivalents must be applied to individual limitations of the claim, not to the invention as a whole.” *Mirror Worlds*, 692 F.3d at 1357 (quoting *Warner-Jenkinson*, 520 U.S. at 29). In his expert report, Dr. Wereley only presents a theory of infringement under the doctrine of equivalents as to the “reagent compartment” limitation. See ECF No. 242-8 Wereley Expert Report ¶¶ 88, 93-94. The Court’s entry of summary judgment of no literal infringement is not based on the “reagent compartment” limitation. Rather, it is based on the “a containment vessel having a top having an opening . . . said opening for receiving a liquid sample and for sealably receiving

Techs., LLC v. VIZIO, Inc., No. SACV181571JVSDFMX, 2020 WL 4258663, at *4 (C.D. Cal. May 14, 2020) (same).

⁹ Genotek argues that a finding of waiver here would violate Federal Rule of Civil Procedure 83(a)(2). ECF No. 242 at 17-18. The Court rejects this argument. The Federal Circuit has affirmed the exclusion of a patentee’s theory of infringement under the doctrine of equivalents where the patentee failed to timely and properly disclose that theory of infringement in its infringement contentions. See, e.g., *Teashot*, 595 F. App'x at 987-88. Indeed, the Federal Circuit has explained: “Because patent local rules are essentially a series of case management orders, a district court may impose any just sanction for the failure to obey them, including refusing to allow the disobedient party to support or oppose designated claims or defenses, or prohibiting that party from introducing designated matters in evidence.” *Phigenix, Inc. v. Genentech, Inc.*, 783 F. App'x 1014, 1016 (Fed. Cir. 2019) (affirming district court’s striking of expert infringement opinions that failed to comply with patent local rules); *accord Taction Tech., Inc. v. Apple Inc.*, No. 21-CV-812 TWR (JLB), 2023 WL 2977728, at *10 (S.D. Cal. Apr. 17, 2023).

1 a sealing cap” limitation. Therefore, because Dr. Wereley’s theory of infringement under
2 the doctrine of equivalents relates to a different limitation, Dr. Wereley’s doctrine of
3 equivalents analysis has no effect on the Court’s non-infringement determination.¹⁰

4 The Court acknowledges that in his expert report, Dr. Wereley states: “Even if the
5 Court were to construe the container as the ‘tube,’ the Spectrum Products would meet the
6 ‘reagent chamber’ limitation under the doctrine of equivalents.” ECF No. 242-8, Wereley
7 Expert Report ¶ 93. However, this assertion made by Dr. Wereley is based on an erroneous
8 understanding of how a patent infringement analysis works. In an infringement analysis
9 under the proper legal standard, the Court does not “construe” accused products or
10 components of accused products. Rather, the Court construes the proper scope of the
11 asserted claims. *See Niazi*, 30 F.4th at 1350–51; *see also Teva*, 574 U.S. at 321 (explaining
12 that “‘construction of a patent, including terms of art within its claim’” is “‘exclusively’
13 for ‘the court’” (quoting *Markman*, 517 U.S. at 390)). The patentee bears the burden of
14 proving infringement based on those properly construed asserted claims. *See Medtronic*,
15 571 U.S. at 193; *Creative Compounds*, 651 F.3d at 1314. In order to satisfy that burden,
16 the patentee “must prove the presence of each and every element or its equivalent in the
17 accused method or device.” *Star Sci.*, 655 F.3d at 1378; *see Uniloc*, 632 F.3d at 1301 (“To
18 prove infringement, the plaintiff bears the burden of proof to show the presence of every
19 element or its equivalent in the accused device.”). As such, it is the patentee’s burden – not
20 the Court’s burden – to identify the relevant components/structures in the accused products
21 that purportedly satisfy the properly construed claim limitations.

22 In an effort to prove infringement in this case, Genotek and its expert chose to
23

24
25 ¹⁰ The Court specifically notes that in his expert report, Dr. Wereley does not assert a
26 theory of infringement under the doctrine of equivalents as to the “containment vessel”
27 limitation. *See* ECF No. 242-8, Wereley Expert Report ¶¶ 46-57. Further, in its
28 infringement contentions, Genotek did not even reserve the right to assert infringement
under the doctrine of equivalents as to the “containment vessel” limitation. *See* ECF No.
231-5, Ex. 3 at 81-88.

1 identify the “cap” and “tube” combined as being the relevant structure of the accused
2 products that purportedly satisfies the “containment vessel” limitation.¹¹ See ECF No. 242
3 at 10-11; ECF No. 242-8 Wereley Decl. ¶¶ 25, 46-47, 89; *see also* ECF No. 231-5, Ex. 3
4 at 87-88. Genotek chose to do so even though this theory of infringement relied on an
5 untimely and erroneous claim construction argument that Genotek waived, and the Court
6 has rejected. And Genotek chose to do so even though the identified structure does not
7 have a “top” (i.e., an uppermost part) with an “opening” for receiving a cap and instead has
8 an enclosed top.

9 In sum, Genotek has waived any theory of infringement under the doctrine of
10 equivalents. Further, regardless of any of Genotek’s arguments regarding infringement
11 under doctrine of equivalents as to the “reagent compartment” limitation, the accused
12 products still fail to satisfy the “containment vessel having a top having an opening . . .
13 said opening for receiving a liquid sample and for sealably receiving a cap” claim limitation
14 based on structure identified by Genotek. Accordingly, Spectrum is entitled to summary
15 judgment of non-infringement as to independent claim 1 of the ’187 Patent. Further,
16 because Spectrum is entitled to summary judgment of non-infringement as to independent
17 claim 1, Spectrum is also entitled to summary judgment of non-infringement as to asserted
18 dependent claims 2, 4, 6-7, 20-21, 23-31, and 33, which all depend from claim 1. *See*
19 *Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1552 n.9 (Fed. Cir. 1989) (“One
20 who does not infringe an independent claim cannot infringe a claim dependent (and thus
21 containing all the limitations of) that claim.”); *see, e.g., Ferring B.V. v. Watson Lab’ys,*
22 *Inc.-Fla.*, 764 F.3d 1401, 1411 (Fed. Cir. 2014) (“Because we hold that the asserted

24
25 ¹¹ In its opposition brief, Genotek only identifies the cap and tube combined as
26 constituting the claimed “containment vessel.” See ECF No. 242 at 8, 10-11. Genotek does
27 not identify any other structure. *See generally id.* Similar, in his expert report, Dr. Wereley
28 only contends that the cap and tube combined constitute the containment vessel. ECF No.
242-8, Wereley Expert Report ¶¶ 47-56. Dr. Wereley does not identify any other structure.
See id.

1 independent claims of Ferring’s patents are not infringed, the asserted dependent claims
2 are likewise not infringed.”); *see also* ECF No. 258 at 1 ¶¶ 2-3 (listing the asserted
3 dependent claims).

4 C. Genotek’s Request for Reconsideration of the Court’s Claim Construction

5 In its opposition brief, Genotek requests that the Court revisit its construction of the
6 claim term “reagent compartment.” ECF No. 242 at 14-15. A motion for reconsideration
7 in a patent case is governed by the law of the regional circuit, here, the Ninth Circuit. *See*
8 *Delaware Valley Floral Grp., Inc. v. Shaw Rose Nets, LLC*, 597 F.3d 1374, 1379 (Fed. Cir.
9 2010). A district court has inherent jurisdiction to modify, alter, or revoke a prior order.
10 *United States v. Martin*, 226 F.3d 1042, 1049 (9th Cir. 2000). The Federal Circuit has
11 specifically explained that “a district court may (and sometimes must) revisit, alter, or
12 supplement its claim constructions . . . to the extent necessary to ensure that final
13 constructions serve their purpose of genuinely clarifying the scope of claims for the finder
14 of fact.” *In re Papst Licensing Digit. Camera Pat. Litig.*, 778 F.3d 1255, 1261 (Fed. Cir.
15 2015) (citing *O2 Micro*, 521 F.3d at 1359; *Pfizer, Inc. v. Teva Pharm., USA, Inc.*, 429 F.3d
16 1364, 1377 (Fed. Cir. 2005)); *see Conoco, Inc. v. Energy & Env’t Int’l, L.C.*, 460 F.3d
17 1349, 1359 (Fed. Cir. 2006) (“[D]istrict courts may engage in ‘rolling claim construction,
18 in which the court revisits and alters its interpretation of the claim terms as its
19 understanding of the technology evolves.’ (quoting *Guttman, Inc. v. Kopykake Enters.,*
20 *Inc.*, 302 F.3d 1352, 1361 (Fed. Cir. 2002)).

21 Reconsideration of a prior order is an “extraordinary remedy, to be used sparingly
22 in the interests of finality and conservation of judicial resources.” *Carroll v. Nakatani*, 342
23 F.3d 934, 945 (9th Cir. 2003); *accord Berman v. Freedom Fin. Network, LLC*, 30 F.4th
24 849, 858–59 (9th Cir. 2022); *see also Marlyn Nutraceuticals, Inc. v. Mucos Pharma GmbH*
25 *& Co.*, 571 F.3d 873, 880 (9th Cir. 2009) (“‘[A] motion for reconsideration should not be
26 granted, absent highly unusual circumstances’”). “Reconsideration [of a prior order]
27 is appropriate if the district court (1) is presented with newly discovered evidence, (2)
28 committed clear error or the initial decision was manifestly unjust, or (3) if there is an

1 intervening change in controlling law.” *School Dist. No. 1J v. ACandS, Inc.*, 5 F.3d 1255,
2 1263 (9th Cir. 1993); accord *Smith v. Clark Cnty. Sch. Dist.*, 727 F.3d 950, 955 (9th Cir.
3 2013). A motion for reconsideration may not be used to relitigate old matters, or to raise
4 arguments or present evidence for the first time that reasonably could have been raised
5 earlier in the litigation. *Exxon Shipping Co. v. Baker*, 554 U.S. 471, 486 n.5 (2008); see
6 *Berman*, 30 F.4th at 859 (“Reconsideration motions may not be used to raise new
7 arguments or introduce new evidence if, with reasonable diligence, the arguments and
8 evidence could have been presented during consideration of the original ruling.” (citing
9 *Kona Enterprises, Inc. v. Estate of Bishop*, 229 F.3d 877, 890 (9th Cir. 2000)); *Williams v.*
10 *Cnty. of San Diego*, 542 F. Supp. 3d 1070, 1071 (S.D. Cal. 2021) (“A motion for
11 reconsideration is not a vehicle to reargue the motion or to present evidence which should
12 have been raised before.”).

13 As an initial matter, Genotek asserts: “If the Court amends its construction [of the
14 term “reagent compartment”], as Spectrum urges, the Court must consider new evidence.”
15 ECF No. 242 at 1; see *id.* at 12-13. The Court has not amended its construction of the claim
16 term “reagent compartment.” Further, the Court notes its entry of summary judgment of
17 non-infringement is not based on the “reagent compartment” limitation. Rather, it is based
18 on the “a containment vessel having a top having an opening . . . said opening for receiving
19 a liquid sample and for sealably receiving a sealing cap” limitation. As such, Genotek’s
20 request for reconsideration of the Court’s construction of “reagent compartment” is moot.

21 Further, Genotek has failed to provide the Court with an adequate basis for
22 reconsideration of the Court’s claim construction. Genotek’s request for reconsideration is
23 based on claim language in dependent claim 30 of U.S. Patent No. 11,572,581 (“the ’581
24 Patent”), which was issued by the United States Patent and Trademark Office (“PTO”) on
25 February 7, 2023. See ECF No. 242 at 3-5, 14-15; U.S. Patent No. 11,572,581 col. 20 ll.
26 62-63 (issued Feb. 7, 2023). Genotek characterizes this as “new evidence,” but there is
27 evidence in the record showing that the dependent claim at issue was first allowed by the
28 examiner back on November 29, 2021 – almost a year before the claim construction hearing

1 in this action and well before the parties filed their joint claim construction chart and their
2 claim construction briefs. *See* ECF No. 254-2, Razai Decl. Ex. 9. A motion for
3 reconsideration “may not be used to raise new arguments or introduce new evidence if,
4 with reasonable diligence, the arguments and evidence could have been presented during
5 consideration of the original ruling.” *Berman*, 30 F.4th at 859; *see Exxon Shipping*, 554
6 U.S. at 486 n.5; *Williams*, 542 F. Supp. 3d at 1071. Genotek fails to adequately explain
7 why it could not rely on the existence of the dependent claim at issue during claim
8 construction in this case based on the November 29, 2021 notice of allowance.

9 Genotek notes that “the PTO had the entire claim construction opinion before it when
10 it allowed claim 30 of the ’581 patent,” and argues that the Court must consider this new
11 prosecution history. ECF No. 242 at 15; *see also* ECF No. 242 at 5; ECF No. 243-8, Ex. 7.
12 Genotek contends: “The PTO either understood the Court’s claim construction the way
13 Genotek interprets it above, or it disagreed with Spectrum’s interpretation.” *Id.* But there
14 are several problems with this assertion regarding the prosecution history. First, Genotek
15 fails to adequately explain the legal significance of providing the examiner with the Court’s
16 claim construction order during prosecution of the ’581 Patent. Genotek implies that in
17 light of the Court’s claim construction order, the examiner could have “withdraw[n] the
18 claims from issuance,” but Genotek fails to provide the Court with any authority
19 demonstrating that this is correct. ECF No. 242 at 5. Genotek states that by the time it
20 provided the examiner with the claim construction order, the claims had already been
21 allowed. *See id.* at 5 (referring to them as “previously allowed claims”). Genotek fails to
22 adequately explain how a district court’s recently issued claim construction order could
23 provide an examiner with a legal basis to reject previously allowed claims. Second,
24 Genotek does not identify any express interpretation or construction by the examiner of the
25 term “reagent compartment.” Rather, Genotek speculates as to how it thinks the examiner
26 might have interpreted the claim term. Third, even assuming the examiner implicitly
27 interpreted the term “reagent compartment” in the manner proposed by Genotek, Genotek
28 fails to explain how the examiner’s purported claim interpretation is material to the claim

1 construction issues in this case. PTO examiners use the “broadest reasonable
2 interpretation” standard to interpret claims, which is different from the *Phillips* standard
3 for claim construction utilized and applied by district courts. *See Seabed Geosolutions*, 8
4 F.4th at 1287 “Under that standard, ‘claims are given their broadest reasonable
5 interpretation consistent with the specification, not necessarily the correct construction
6 under the framework laid out in *Phillips*.’” *Id.* (quoting *PPC Broadband, Inc. v. Corning*
7 *Optical Commc’ns RF, LLC*, 815 F.3d 734, 742 (Fed. Cir. 2016); *see also MiMedx Grp.,*
8 *Inc. v. Tissue Transplant Tech., Ltd.*, 354 F. Supp. 3d 742, 750 (W.D. Tex. 2018)
9 (explaining that “the purpose behind the PTO’s use of the BRI standard is to ‘allow the
10 examiner and the applicant to explore the broadest possible scope of the claim,’ while a
11 federal court’s use of the *Phillips* standard is to “search ‘for the one “correct”
12 interpretation”” (quoting *Flo Healthcare Sols., LLC v. Kappos*, 697 F.3d 1367, 1378 (Fed.
13 Cir. 2012), *overruled on other grounds by Williamson v. Citrix Online, LLC*, 792 F.3d 1339
14 (Fed. Cir. 2015)). As such, the Court denies Genotek’s request for reconsideration.

15 **VI. SPECTRUM’S MOTION FOR SUMMARY JUDGMENT OF NON-** 16 **INFRINGEMENT OF THE ’646 PATENT**

17 Spectrum argues that it is entitled to summary judgment of non-infringement as to
18 the ’646 Patent because Genotek cannot show that the accused products preserve cells of a
19 biological sample as required by the claims of the ’646 Patent. ECF No. 231-1 at 14-18. In
20 response, Genotek argues that Spectrum’s motion should be denied because there is at least
21 a genuine dispute of material fact over the “preserving a biological sample” claim
22 limitation. ECF No. 242 at 18-25.

23 Independent claim 1 of the ’646 Patent claims: “A kit for collecting and preserving
24 a biological sample.” ’646 Patent col. 22 ll. 16. At claim construction, the Court held that
25 the preamble of independent claim 1 is limiting. ECF No. 177 at 62. In addition, the Court
26 construed the claim term “preserving a biological sample” as “preventing cells in the
27 biological sample from having their antigens degraded such that they can be purified or
28

enriched based on their antigens, and preventing alterations in the cellular epigenome.” *Id.* at 65.

As an initial matter, the parties acknowledge and agree that the Court’s construction of the term “preserving a biological sample” is two-part. *See* ECF No. 242 at 19-23; ECF No. 254 at 6-7. First, the Court’s construction for that term requires that the claimed “kit” “prevent[s] cells in the biological sample from having their antigens degraded such that they can be purified or enriched based on their antigens.” ECF No. 177 at 65. Second, the Court’s construction requires that the claimed “kit” “prevent[s] alterations in the cellular epigenome.” *Id.* Thus, in order to raise a genuine dispute of material fact as to the “preserving a biological sample” limitation, Genotek must present sufficient evidence from which a reasonable jury could conclude that both of those requirements in the Court’s claim construction are satisfied by the accused products. *See Advanced Steel Recovery*, 808 F.3d at 1317.

A. “preventing cells in the biological sample from having their antigens degraded such that they can be purified or enriched based on their antigens”

Genotek asserts that the accused products “prevent[] cells in the biological sample from having their antigens degraded such that they can be purified or enriched based on their antigens.” *See* ECF No. 242 at 19-20. To support this assertion, Genotek primarily relies on the opinions of its expert, Dr. Metzker. *See id.*

In his expert report, Dr. Metzker opines that the accused products’ solution¹² prevents cells in the biological sample from having their antigens degraded such that they

¹² The Court declines to refer to the accused products’ solution as a “preservative” as Dr. Metzker does in his expert report. *See, e.g.*, ECF No. 242-7, Metzker Expert Report ¶¶ 122, 126, 130. The Court notes that elsewhere in his report Dr. Metzker refers to the composition at issue as “reagents” or the “blue stabilizing solution.” *See id.* ¶¶ 48-50. Further, the Court will not refer to the samples in Metzker’s test as the “non-preserved and preserved samples” as Dr. Metzker does. *See, e.g., id.* ¶ 128. Rather, the Court will refer to the samples as samples with the solution and samples without the solution.

1 can be purified or enriched based on their antigens. ECF No. 242-7, Metzker Expert Report
2 ¶ 130. To support this opinion, Dr. Metzker relies on the results of testing performed by
3 the Applied Biomedical Science (“ABS”) Institute in San Diego. *See id.* ¶¶ 122-29. Dr.
4 Metzker explains this testing as follows:

5 [T]wo donors provided saliva samples directly into Spectrum SDNA-
6 1000 devices. Each donor provided six (6) saliva samples according to Step 1
7 of the SDNA-1000 IFU. Three of the six samples for each donor were then
8 processed according to Step 2 SDNA-1000 IFU, 150 to release the . . . solution
9 into the saliva samples. . . . The remaining three samples for each donor were
10 capped without engaging the valve, and therefore the . . . solution stayed in
11 the cap.

12 [T]hree timepoints were evaluated for [the samples] for each donor: 0-
13 hour, 24-hour, and 72-hour, which incubated at room temperature.

14 *Id.* 123-24. Based on the resulting data from these tests, Dr. Metzker opines: “these data
15 provide strong evidence that the Spectrum Product[’s] solution protects the TLR2 antigen
16 from degradation.” *Id.* ¶ 128 (explaining that the sample with the solution “show[s] a high
17 percentage (41.1%) of TLR2⁺ aggregate cells whereas no such cells were found in the”
18 sample without the solution).

19 But the problem with this opinion is that TLR2 is not the only antigen at issue in the
20 testing. The testing also involved CD4, CD45, and EpCAM antigens. *See id.* ¶ 122, Ex. C.
21 Dr. Metzker does not provide any specific analysis of the data related to those three
22 antigens in his report. But importantly, Dr. Metzker concedes that “the general trend for all
23 data in Exhibit C are the [samples with the solution] have lower cell percentages compared
24 with” the samples without the solution. *Id.* ¶ 128. Indeed, a review of the testing results
25 related to CD4, CD45, and EpCAM show that with respect to those antigens, there were
26 many fewer cells positive for those antigens in the samples with the solution than there
27 were in the samples without any solution after 24 and 72 hours. *See id.* ¶ 128, Ex. C. For
28 example, according to the results in Exhibit C to the Metzker Report, at 24 hours, the

sample without the solution from Donor 1 showed a much higher presence of cells positive for CD45 (11.0% stained and 0.10% unstained) compared to the sample with the solution (0.57% stained and 0.08% unstained). *See id.* Ex. C at 93; *see also id.* Ex. C at 94, 98, 99, 100.¹³ In assessing this data, the Court is simply employing the same method utilized by Dr. Metzker in his report – i.e., comparing the cell percentage numbers in the gates drawn by Genotek’s other experts between the solution and non-solution samples from the same donor. And this assessment of the data is consistent with Dr. Metzker’s concession that “the general trend” is that the “cell percentages” are “lower” for the samples with the solution. *Id.* ¶ 128. This data in Dr. Metzker’s report regarding CD4, CD45, and EpCAM and his concession regarding that data is significant because this shows via Dr. Metzker’s own testing that adding the solution to the samples actually increased the degradation of many antigens rather than preventing degradation. *See id.*

Further, these test results are consistent with the fact that in his expert report, Dr. Metzker also opines that the accused products satisfy the chemistry limitations in Claim 1 of the ’187 Patent. *See* ECF No. 242-7, Metzker Expert Report ¶¶ 58-80. The specification of the ’187 Patent explains: “When sputum is mixed with a composition of the present invention, cells are disrupted, nucleic acids are liberated from the cells, membranous material is solubilized, proteins are stripped from the nucleic acids, and protein digestion begins.” ’187 Patent col. 13 ll. 38-42; *see also Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1353 (Fed. Cir. 2016) (“When a patentee ‘describes the features of the ‘present invention’ as a whole,’ he implicitly alerts the reader that ‘this description limits the scope of the invention.’” (quoting *Regents of Univ. of Minnesota v. AGA Med. Corp.*, 717 F.3d 929, 936 (Fed. Cir. 2013)); *Techtronic Indus. Co. v. Int’l Trade Comm’n*, 944

¹³ As another example, Exhibit C shows that at 72 hours, the sample without the solution from Donor 2 showed a much higher presence of cells positive for CD45 and EpCAM (0.20% unstained, 18.1% stained CD45, and 20.7% stained EpCAM) compared to the sample with the solution (0.34% unstained, 2.83% stained CD45, and 0.65% stained EpCAM). *See* ECF No. 242-7, Metzker Expert Report Ex. C at 100.

1 F.3d 901, 907 (Fed. Cir. 2019) (“It is axiomatic that, where the specification ‘describes
2 “the present invention” as having [a] feature,’ that representation may disavow contrary
3 embodiments.”). By asserting that accused products practice the claims of the ’187 Patent,
4 Dr. Metzker is conceding that the accused products’ solution performs in the manner
5 described by the ’187 Patent’s specification. And Spectrum also concedes that the accused
6 solution performs in this manner, *see* ECF No. 231-1 at 1-2, 14-17, meaning that it is not
7 only Dr. Metzker’s opinion, but it is an undisputed fact in this case that the accused solution
8 performs in that manner.

9 That Dr. Metzker’s own testing demonstrates that the solution increases degradation
10 of CD4, CD45, and EpCAM is consequential because the Court’s construction of the
11 relevant claim term requires that the accused solution prevent “cells in the biological
12 sample from having their antigens degraded.” ECF No. 177 at 65. The Court’s claim
13 construction says “cells” and “antigens” plural, not one type of antigen or cell. As such,
14 even crediting as true Dr. Metzker’s opinion that the accused products’ solution protects
15 TLR2 antigens from degradation,¹⁴ that is insufficient to satisfy the Court’s construction
16 of the relevant claim term when the other evidence in Dr. Metzker’s report demonstrates
17 that the accused products’ solution increases the degradation of other antigens. Because the
18 testimony from Dr. Metzker along with the data in his report demonstrate that the accused
19

20
21 ¹⁴ Although for purposes of this summary judgment analysis, the Court credits as true
22 Dr. Metzker’s opinions regarding TLR2 antigens, *see Charles Mach. Works, Inc. v.*
23 *Vermeer Mfg. Co.*, 723 F.3d 1376, 1380 (Fed. Cir. 2013), even those opinions are highly
24 problematic. In his expert report, in assessing TLR2, Dr. Metzker focuses entirely on
25 “TLR2⁺ Aggregates” data while entirely ignoring the “TLR2⁺ Singlets” data shown in the
26 graphs at issue. ECF No. 242-7, Metzker Expert Report ¶ 128. In his report, Dr. Metzker
27 provides no explanation for why the “TLR2⁺ Singlets” data should be ignored. *See id.*
28 Exhibit C to Dr. Metzker’s report shows that at 72 hours, the sample without the solution
from Donor 2 showed a much higher presence of cells positive for “TLR2⁺ Singlets”
(22.5% stained and 0.56% unstained) compared to the sample with the solution (0.32%
stained and 0.095% unstained). *See* ECF No. 242-7, Metzker Expert Report Ex. C at 102.

1 products increase, rather than prevent, the degradation of CD4, CD45, and EpCAM
2 antigens, no reasonable jury could conclude the accused products satisfy the “preserving a
3 biological sample” claim limitation as construed by the Court.¹⁵

4 At the hearing, Genotek argued that Dr. Metzker’s opinions regarding TLR2 should
5 be sufficient to meet the Court’s claim construction regardless of the data as to CD4, CD45,
6 and EpCAM. *See* ECF No. 312 at 31-38. The Court disagrees. To support its argument,
7 Genotek relies on a preferred embodiment described in the specification of the ’187 Patent
8 where the inventors isolated T-cells from saliva and confirmed that the T-cell’s antigens
9 remained intact by just targeting CD4, a single type of antigen. *See* ’646 Patent col. 18 l.64-
10 col. 19 l. 40; *see also* ECF No. 242-7, Metzker Report ¶ 117. But the testing in Dr.
11 Metzker’s report is not analogous to that embodiment in the specification. Dr. Metzker did
12 not simply isolate skin cells and then test whether the accused solution preserves TLR2
13 and find that indeed it does. Rather, he tested whether the accused solution preserves TLR2,
14 CD4, CD45, and EpCAM, and came back with data demonstrating that the solution
15 increases degradation of CD4, CD45, and EpCAM, meaning that the solution at issue
16 increases the degradation of antigens rather than preventing it. This cannot satisfy the
17 Court’s claim construction.

18 At the hearing, Genotek also argued that the numbers in the charts in Exhibit C are
19 not important, and, instead, what is important is the fluorescence displayed in the charts.
20 ECF No. 312 at 14-15, 17, 18-19. The Court rejects this argument as it has no basis at all
21 in the actual analysis that is presented in Dr. Metzker’s report. In Exhibit C to his report,
22 Genotek’s other experts drew the gates at issue, and they set forth the cell percentage
23

24
25 ¹⁵ In its opposition, Genotek cites to certain evidence and contends that this evidence
26 “shows that there is, at a minimum, reason to doubt the veracity of Spectrum’s contentions
27 about the extensive damage that its [solution] causes cells.” ECF No. 242 at 21-23. The
28 problem with this argument is that in the above analysis, the Court is not relying on
Spectrum’s statements regarding the effects of its solution. Rather, the Court is relying on
the testimony and data from Genotek’s own expert regarding the effects of the solution.

1 numbers corresponding with those gates. *See* ECF No. 242-7, Metzker Expert Report at
 2 89. And in his report, Dr. Metzker expressly cites to those cell percentage numbers (for
 3 example, 41.1%) to support his opinions. *See id.* ¶ 128 (“[T]he [sample with solution] show
 4 a high percentage (41.1%) of TLR2⁺ aggregate cells whereas no such cells were found in
 5 the [sample with no solution]”). Dr. Metzker makes no reference to the “fluorescence”
 6 analysis described by Genotek at the hearing. *See id.* Genotek’s discussion of
 7 “fluorescence” at the hearing is nothing more than attorney argument. “[I]n order to defeat
 8 a properly supported motion for summary judgment,” a plaintiff “must present affirmative
 9 evidence.” *Anderson*, 477 U.S. at 257. “Attorney argument is not evidence.” *Icon Health*
 10 *& Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017); *accord FastShip, LLC*
 11 *v. United States*, 892 F.3d 1298, 1309 (Fed. Cir. 2018). As such, Genotek’s attorney
 12 argument regarding “fluorescence” is insufficient to raise a triable issue of fact.¹⁶

13 Similarly, at the hearing, Genotek argued that it was the “quality” of the cells
 14 remaining in the samples that mattered, not the number of cells. ECF No. 312 at 16-17, 25-
 15 27. The Court rejects this argument as again Genotek’s “quality over quantity” argument
 16 has no basis whatsoever in Dr. Metzker’s expert report. In his expert, Dr. Metzker focused
 17 on cell percentage numbers (for example, “41.1%”) to support his opinions. *See* ECF No.
 18 242-7, Metzker Expert Report ¶ 128. As such, Dr. Metzker’s own analysis focused on
 19 quantity. Moreover, that Genotek’s “quality” argument has no basis in Dr. Metzker’s actual
 20 analysis is demonstrated by Genotek’s reliance and focus on paragraph 135 of Dr.
 21 Metzker’s report to support its contention. Paragraph 135 of Dr. Metzker’s report is from
 22 _____

23
 24 ¹⁶ Further, even if the Court accepted Genotek’s contention that it is not the numbers
 25 in the charts that matter, but, instead, whether visually can you see “more dots in that box
 26 . . . than otherwise,” the data still supports the conclusion that the solution increases the
 27 degradation of antigens. For example, Exhibit C shows that at 72 hours, the sample without
 28 the solution from Donor 2 contained a lot “more dots” for CD45 and EpCAM in the gates
 drawn by Genotek’s experts than in the gates for the sample with the solution. *See* ECF
 No. 242-7, Metzker Expert Report Ex. C at 100; *see also id.*, Ex. C at 93, 94, 96, 98, 99,
 101, 102.

1 a different section of his expert report addressing a different portion of the Court’s claim
2 construction for this term. *See id.* ¶ 135 (contained in section B.1.b entitled “The Spectrum
3 Products’ [solution] present[s] alterations in the cellular epigenome”). In the section of his
4 expert report that addresses the portion of the Court’s claim construction at issue, Dr.
5 Metzker makes no reference to paragraph 135 of his expert report. *See id.* ¶¶ 114-30. As
6 such, Genotek’s “quality over quantity” argument is untethered to Dr. Metzker’s actual
7 analysis and is again nothing more than attorney argument unsupported by any evidence in
8 the record. *See Icon Health & Fitness*, 849 F.3d at 1043 (“Attorney argument is not
9 evidence.”); *FastShip*, 892 F.3d at 1309 (same). And it is insufficient to raise a triable issue
10 of fact. *See Anderson*, 477 U.S. at 257.

11 In an effort to create a triable issue of fact, Genotek also notes that in his expert
12 report, Dr. Metzker explains that the reagent ingredients in Spectrum’s solution include
13 antimicrobial ingredients and alcohol. ECF No. 242 at 19-20 (citing ECF No. 242-7,
14 Metzker Expert Report ¶¶ 119, 121). Genotek notes that the ’646 Patent recognizes that
15 antimicrobial agents “‘prevent damage to cells from microbial contamination.’” ECF No.
16 242 at 19; *accord* ’646 Patent col. 17 ll. 15-16. Genotek also notes that the ’646 Patent
17 teaches that chemical fixing agents, such as alcohol, “are ‘used to alter cell components
18 such that the cells resist degradation.’” ECF No. 242 at 20; *accord* ’646 Patent col. 16 ll.
19 48-50.

20 But the problem with this argument is that those ingredients are just that – they are
21 “ingredients.” They are not the entire solution. Alcohol by itself might be a chemical fixing
22 agent, and antimicrobial ingredients by themselves might prevent damage to cells. But the
23 accused solution is not alcohol by itself or antimicrobial ingredients by themselves. The
24 solution is all the ingredients contained in the accused products’ reagent solution combined.
25 And the data and testimony from Genotek’s own expert shows that the accused products’
26 solution (with all of its ingredients combined) increases the degradation of antigens rather
27 than preventing it. And Dr. Metzker’s discussion of certain specific ingredients in the
28 accused products’ solution does not change that fact. In sum, summary judgment of no

1 infringement of Claim 1 of the '646 Patent is appropriate because no reasonable jury could
2 conclude, based on the evidence presented by Genotek, that the accused products satisfy
3 the “prevent[] cells in the biological sample from having their antigens degraded such that
4 they can be purified or enriched based on their antigens” requirement in the Court’s
5 construction of the “preserving a biological sample” claim limitation.

6 B. “preventing alterations in the cellular epigenome”

7 Genotek asserts that the accused products “prevent[] alterations in the cellular
8 epigenome.” ECF No. 242 at 20-21. To support this assertion, Genotek relies solely on the
9 opinions of its expert Dr. Metzker. *See id.*

10 In his expert report, Dr. Metzker opines that the accused products’ solution prevents
11 alterations in the cellular epigenome. ECF No. 242-7, Metzker Expert Report ¶ 138. To
12 support this opinion, Dr. Metzker describes testing that was performed, and Dr. Metzker
13 asserts that the DNA methylation data from that testing “demonstrate no alteration in the
14 cellular epigenome caused by demethylation” in the samples with the solution. *Id.* ¶¶ 133-
15 37 (“Overall, data show that the [samples with solution] exhibit consistent methylation
16 patterning, even after three days at room temperature.”). But this is insufficient to
17 demonstrate that the accused products’ solution prevents alterations in the cellular
18 “epigenome” within the context of the '646 Patent.

19 As Dr. Metzker acknowledges in his report, the '646 Patent provides a definition of
20 the term “epigenome.” ECF No. 242-7, Metzker Expert Report ¶ 131. The specification
21 of the '646 Patent provides:

22 The “epigenome” means the state or pattern of alteration of genomic DNA by
23 covalent modification of the DNA or of proteins bound to the DNA. Examples
24 of such alteration include methylation at the 5 position of cytosine in a CpG
25 dinucleotide, acetylation of lysine residues of histones, and other heritable or
26 non-heritable changes that do not result from changes in the underlying DNA
27 sequence.
28

1 '646 Patent col. 16 ll. 27-33. *See Phillips*, 415 F.3d at 1316 (“[T]he specification may
 2 reveal a special definition given to a claim term by the patentee In such cases, the
 3 inventor’s lexicography governs.”); *Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d
 4 1322, 1329 (Fed. Cir. 2009) (explaining that a patentee acts as his own lexicographer when
 5 the patentee “‘clearly set[s] forth a definition of the disputed claim term in either the
 6 specification or prosecution history.’”); *see, e.g., Biogen MA Inc. v. EMD Serono, Inc.*, 976
 7 F.3d 1326, 1336 (Fed. Cir. 2020).¹⁷

8 Here, the specification explains that “epigenome” encompasses the state or pattern
 9 of alteration of genomic DNA by: (1) “covalent modification of the DNA”; or (2) covalent
 10 modification “of proteins bound by the DNA.” ’646 Patent col. 16 ll. 27-29. And the
 11 specification then lists two explicit examples of what constitutes “alterations” to the
 12 epigenome: “methylation at the 5 position of cytosine in a CpG dinucleotide” and
 13 “acetylation of lysine residues of histones.”¹⁸ *Id.* at col. 16 ll. 29-33. Thus, in order to
 14 prevent alterations in the cellular epigenome within the context of the ’646 Patent, the
 15 accused products’ solution must at the very least prevent both “methylation at the 5 position
 16 of cytosine in a CpG dinucleotide” and “acetylation of lysine residues of histones.” *See*
 17 *id.*; *see also id.* at col. 18 ll. 26-27 (“Histones must be chemically fixed to the DNA in order
 18 to be studied.”).

21
 22 ¹⁷ Genotek notes that the Court’s claim construction order does not contain a definition
 23 of the word “epigenome.” ECF No. 242 at 6. But this is of no consequence here because in
 24 his report Dr. Metzker asserts that the above passage in the specification of the ’646 Patent
 25 sets forth the proper definition for the term “epigenome.” *See* ECF No. 242-7, Metzker
 26 Expert Report ¶ 131. As such, the Court’s analysis of this issue is based on what Dr.
 Metzker asserts is the proper definition of the term “epigenome.”

27 ¹⁸ In his expert report, Dr. Metzker explains that “histones” are proteins that form
 28 “chromatin,” and “chromatin” is what forms chromosomes. ECF No. 242-7, Metzker
 Expert Report ¶ 35.

1 The cited testing in Dr. Metzker’s report only concerns DNA methylation.¹⁹ *See* ECF
 2 No. 242 at 20 (referring to testing as “DNA methylation testing”); ECF No. 242-7, Metzker
 3 Expert Report ¶¶ 133-37 (referring to the data as “DNA methylation data”). It doesn’t
 4 address histone acetylation. Indeed, at the hearing, Genotek conceded that Dr. Metzker did
 5 not do a histone acetylation test. ECF No. 312 at 45. As such, Dr. Metzker’s opinions are
 6 insufficient to demonstrate that the accused products prevent alterations in the cellular
 7 “epigenome” within the context of the ’646 Patent. Further, because Dr. Metzker’s
 8 opinions are the only evidence Genotek relies on to demonstrate that the accused products
 9 prevent alterations in the cellular epigenome, this is another reason why Genotek has failed
 10 to raise a triable issue of material fact as to the “preserving a biological sample”
 11 limitation.²⁰

12 C. Conclusion

13 In sum, Spectrum is entitled to summary judgment of non-infringement as to
 14 independent claim 1 of the ’646 Patent. Further, because Spectrum is entitled to summary
 15

16
 17 ¹⁹ The Court acknowledges that in his expert report, Dr. Metzker states: “Saliva
 18 collection devices with stabilizing solutions are commonly used for epigenetic analysis and
 19 are not thought to alter the cellular epigenome.” ECF No. 242-7, Metzker Expert Report ¶
 20 132. But the publication that Dr. Metzker cites to support this opinion also only focuses on
 DNA methylation. *See id.* (citing publication entitled “DNA methylation analysis from
 saliva samples for epidemiological studies”).

21 ²⁰ Moreover, other evidence in the record states that the solution in the accused
 22 products “will destroy or disable the proteins that are attached to the nucleic acids.” ECF
 23 No. 231-6, Ex. 4, Gaeta Depo. at 34. Spectrum criticizes Dr. Gaeta’s testimony on the
 24 grounds that he never performed any testing to determine whether the solution alters
 cellular epigenomes. ECF No. 242 at 18. But on the specific issue of proteins bound to the
 25 DNA, Dr. Metzker didn’t perform any testing either to rebut Dr. Gaeta’s statements. In
 addition, again, Dr. Metzker opines that the accused products satisfy the chemistry
 26 limitations of the asserted claims of the ’187 Patent. *See* ECF No. 242-7, Metzker Expert
 Report ¶¶ 58-80. Consistent with Dr. Gaeta’s testimony, the specification of the ’187 Patent
 27 explains that the claimed reagent composition liberates nucleic acid from cells, strips
 28 proteins from nucleic acid, and digests those proteins. *See* ’187 Patent col. 13 ll. 38-42.

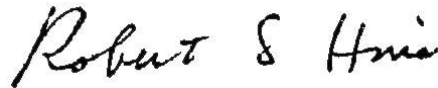
judgment of non-infringement of independent claim 1, Spectrum is also entitled to summary judgment of non-infringement as to asserted dependent claims 4-8 and 11-12, which all depend from claim 1. *See Wahpeton Canvas*, 870 F.2d at 1552 n.9; *see, e.g., Ferring*, 764 F.3d at 1411; *see also* ECF No. 258 at 1 ¶¶ 4-5 (listing the asserted dependent claims).²¹

VII. CONCLUSION

For the reasons above, the Court grants Spectrum's motion for summary judgment that the accused products do not infringe the '187 Patent and the accused products do not infringe the '646 Patent.

SO ORDERED.

Dated: May 2, 2023



Hon. Robert S. Huie
United States District Judge

²¹ To support its motion for summary judgment of non-infringement of the '646 Patent, Spectrum attached to its reply brief a declaration from its technical expert, Dr. Lisa Nichols. *See* ECF No. 254-3, Nichols Decl. Genotek argues that it is improper to submit new evidence as part of a reply brief. ECF No. 242 at 25 n.2. "Ordinarily, 'where new evidence is presented in a reply to a motion for summary judgment, the district court should not consider the new evidence without giving the non-movant an opportunity to respond.'" *S.E.C. v. Platforms Wireless Int'l Corp.*, 617 F.3d 1072, 1088 (9th Cir. 2010); *accord Townsend v. Monster Beverage Corp.*, 303 F. Supp. 3d 1010, 1027 (C.D. Cal. 2018). The non-infringement analysis above does not cite to or rely on any opinions in the Nichols declaration, and, therefore, the issue is moot.

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**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA**

DNA GENOTEK INC., a Canadian
Corporation,

Plaintiff,

v.

SPECTRUM SOLUTIONS L.L.C.,
a Utah Limited Liability Company,

Defendant.

Case No. 3:21-cv-0516-RSH-DDL

FINAL JUDGMENT

AND RELATED COUNTERCLAIMS

CASE No. 3:21-cv-0516-RSH-DDL
FINAL JUDGMENT

1 Plaintiff DNA Genotek (“Genotek”) alleged that Spectrum Solutions L.L.C.
2 (“Spectrum”) infringes U.S. Patent No. 10,619,187 (“the ’187 patent”) and U.S.
3 Patent No. 11,002,646 (“the ’646 patent”) (collectively, “the Patents-in-Suit”).
4 Spectrum asserted a counterclaim for declaratory judgment of non-infringement of
5 the Patents-in Suit. Doc. No. 341.

6 The Court granted Spectrum’s Motion for Summary Judgment of Non-
7 Infringement of the Patents-in-Suit. Doc. No. 315.

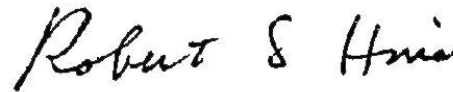
8 In view of the foregoing, **IT IS HEREBY ORDERED AND ADJUDGED**
9 that:

- 10 1. Final judgment of non-infringement is entered in favor of Spectrum on
11 U.S. Patent Nos. 10,619,187 and 11,002,646.
- 12 2. DNA Genotek shall take nothing by way of its complaint.
- 13 3. Spectrum is awarded its costs as taxed by the Clerk.

14 Pursuant to Federal Rule of Civil Procedure 58, the Court directs the Clerk to
15 enter this Final Judgment as set forth above.

16 **SO ORDERED.**

17
18 Dated: June 7, 2023



Hon. Robert S. Huie
United States District Judge



US010619187B2

(12) **United States Patent**
Birnboim

(10) **Patent No.:** **US 10,619,187 B2**

(45) **Date of Patent:** ***Apr. 14, 2020**

(54) **COMPOSITIONS AND METHODS FOR OBTAINING NUCLEIC ACIDS FROM SPUTUM**

(56) **References Cited**

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(71) Applicant: **DNA GENOTEK INC.**, Kanata (CA)

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(72) Inventor: **H. Chaim Birnboim**, Ottawa (CA)

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(73) Assignee: **DNA GENOTEK INC.**, Ottawa (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 351 days.

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This patent is subject to a terminal disclaimer.

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(22) Filed: **Nov. 7, 2016**

(Continued)

(65) **Prior Publication Data**

US 2017/0152545 A1 Jun. 1, 2017

Primary Examiner — Sally A Merkling

Related U.S. Application Data

(74) *Attorney, Agent, or Firm* — Lathrop GPM LLP; James H. Velema, Esq.

(63) Continuation of application No. 14/549,344, filed on Nov. 20, 2014, now Pat. No. 9,523,115, which is a (Continued)

(57) **ABSTRACT**

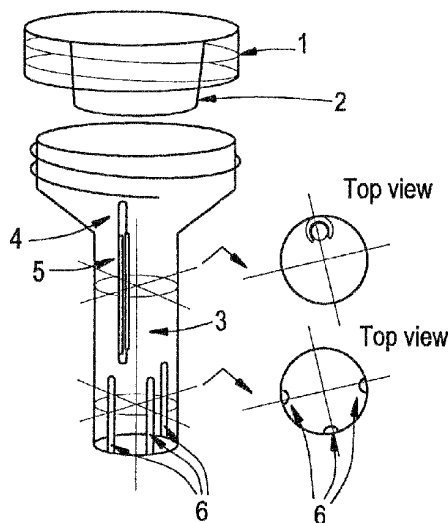
(51) **Int. Cl.**
C12Q 1/6806 (2018.01)
B01L 3/00 (2006.01)
C12N 15/10 (2006.01)

The present invention relates to compositions and methods for preserving and extracting nucleic acids from saliva. The compositions include a chelating agent, a denaturing agent, buffers to maintain the pH of the composition within ranges desirable for DNA and/or RNA. The compositions may also include a reducing agent and/or antimicrobial agent. The invention extends to methods of using the compositions of the invention to preserve and isolate nucleic acids from saliva as well as to containers for the compositions of the invention.

(52) **U.S. Cl.**
CPC **C12Q 1/6806** (2013.01); **B01L 3/502** (2013.01); **B01L 3/5082** (2013.01); (Continued)

(58) **Field of Classification Search**
CPC C12Q 1/6806; B01L 3/5082; B01L 3/502; B01L 2300/047; B01L 2300/046; (Continued)

36 Claims, 11 Drawing Sheets



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Related U.S. Application Data

continuation of application No. 12/338,873, filed on Dec. 18, 2008, now abandoned, which is a continuation of application No. 10/455,680, filed on Jun. 5, 2003, now Pat. No. 7,482,116.

- (60) Provisional application No. 60/386,399, filed on Jun. 7, 2002, provisional application No. 60/386,397, filed on Jun. 7, 2002, provisional application No. 60/386,398, filed on Jun. 7, 2002.

(52) U.S. Cl.

CPC *C12N 15/1003* (2013.01); *B01L 2300/042* (2013.01); *B01L 2300/046* (2013.01); *B01L 2300/047* (2013.01); *B01L 2300/0672* (2013.01); *B01L 2300/0832* (2013.01); *B01L 2400/0683* (2013.01)

(58) Field of Classification Search

CPC *B01L 2300/0672*; *B01L 2300/042*; *B01L 2300/0832*; *B01L 2400/0683*; *C12N 15/1003*

See application file for complete search history.

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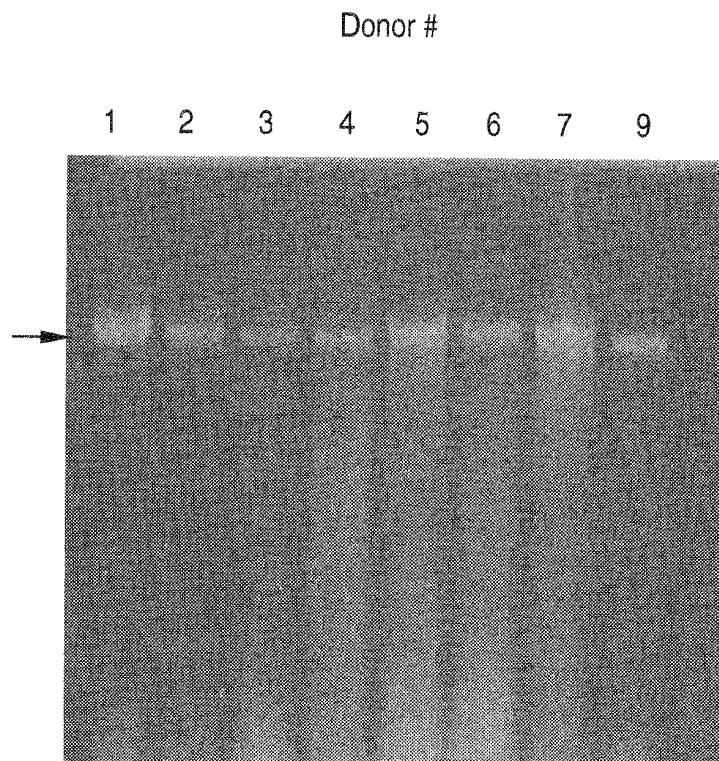
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FIG. 1



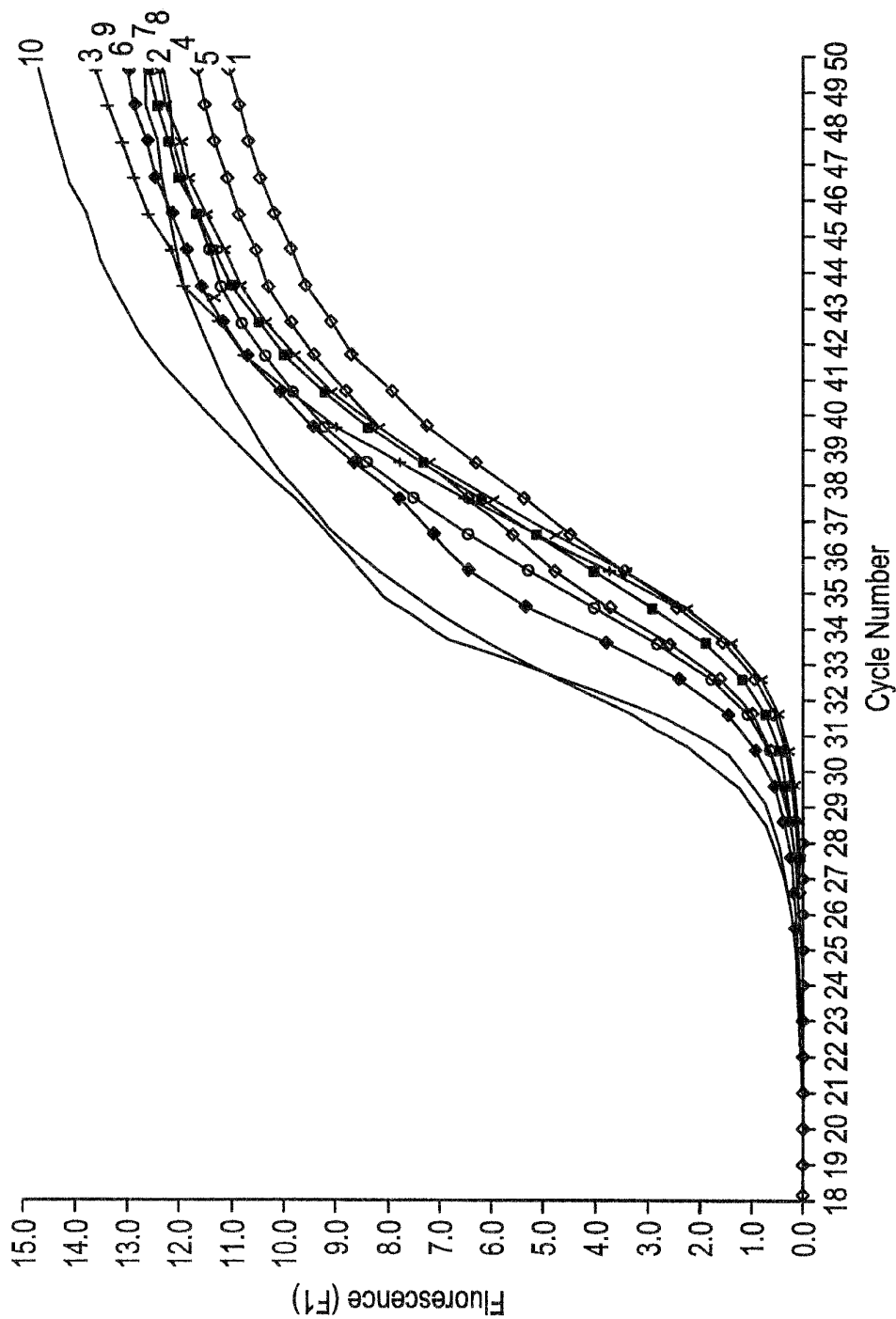
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FIG. 2



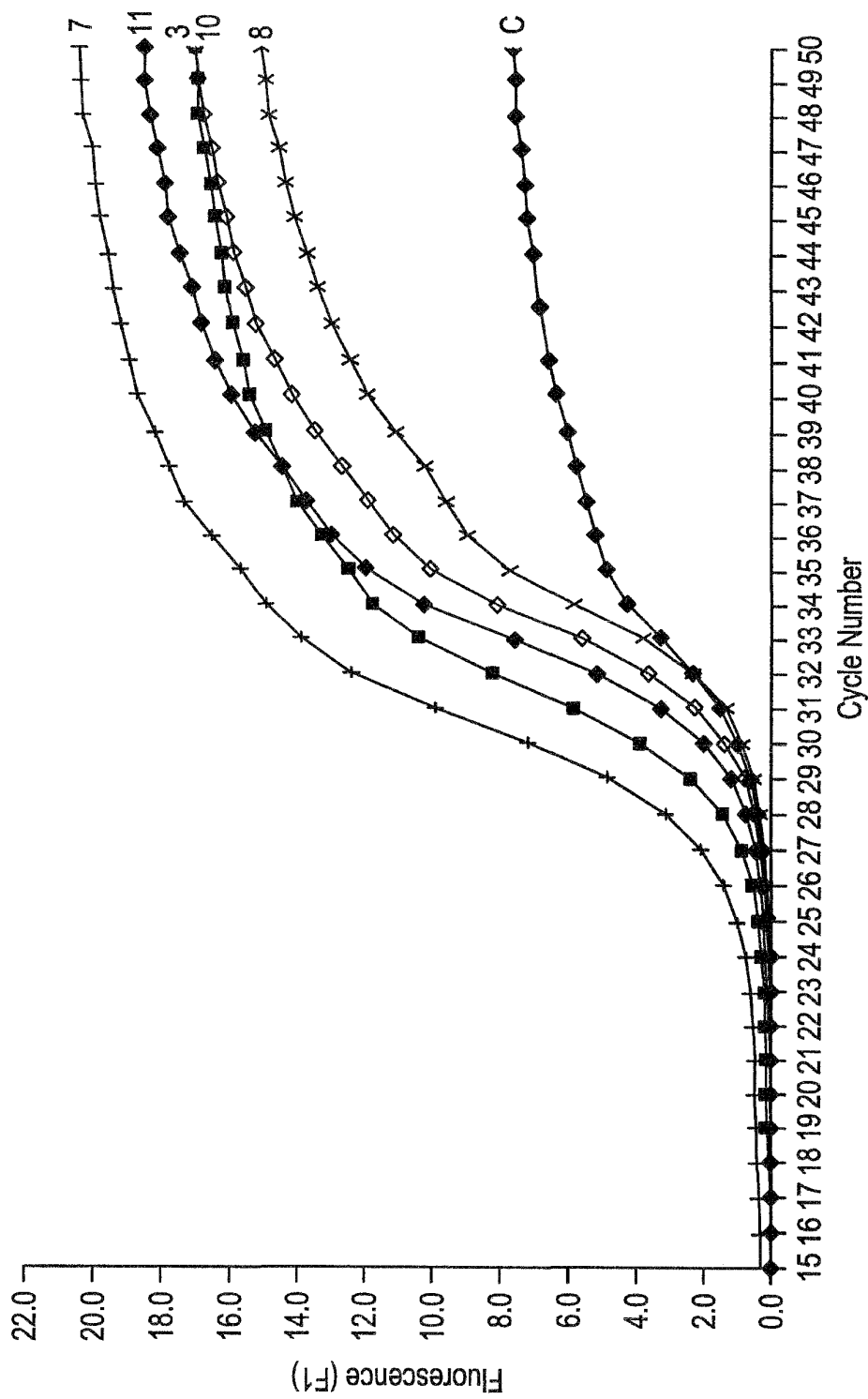
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FIG. 3



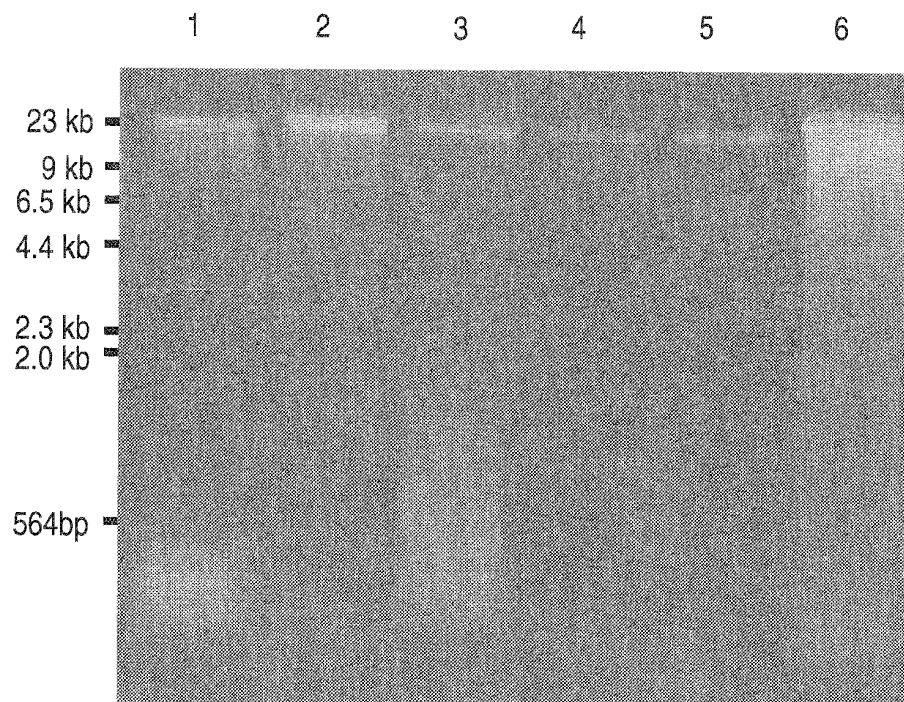
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FIG. 4



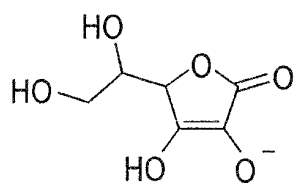
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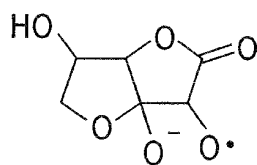
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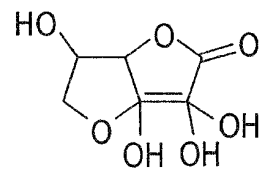
FIG. 5



Ascorbate anion



Ascorbate radical



Dehydroascorbic acid

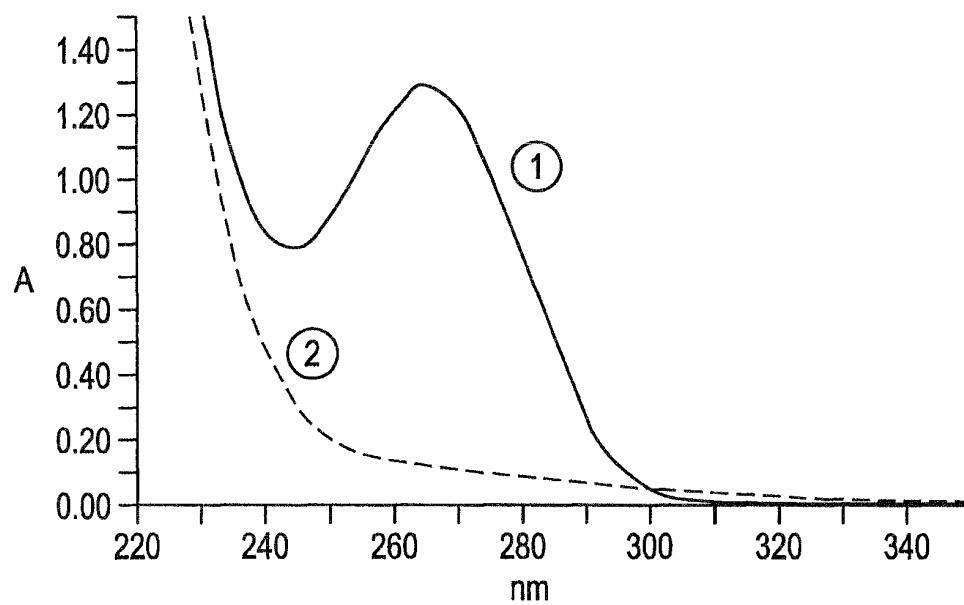
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FIG. 6



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FIG. 7

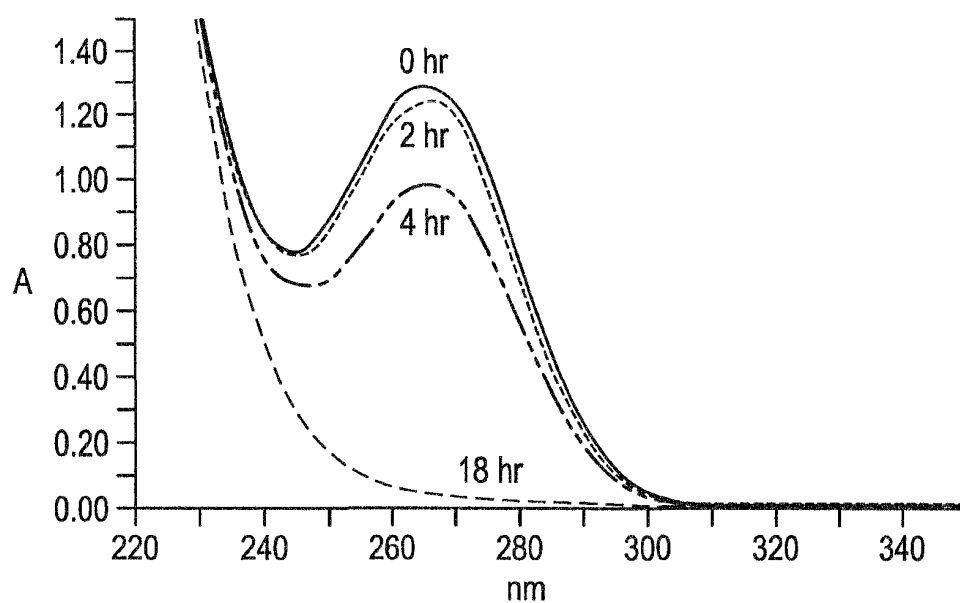


FIG. 8

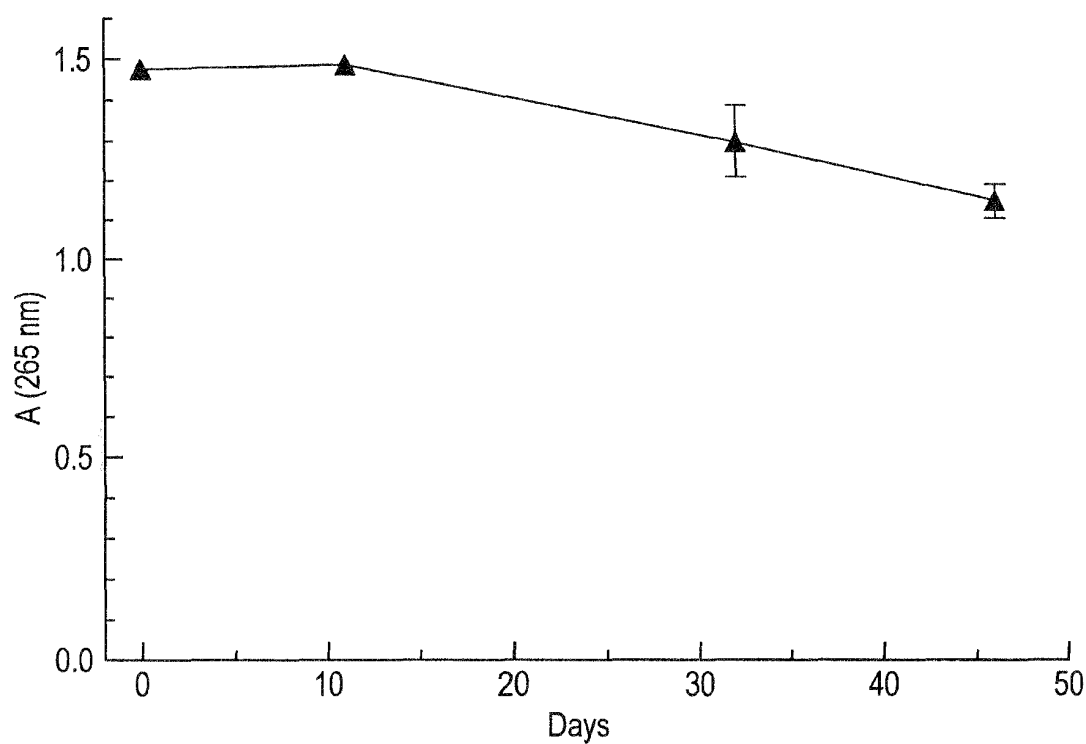


FIG. 9

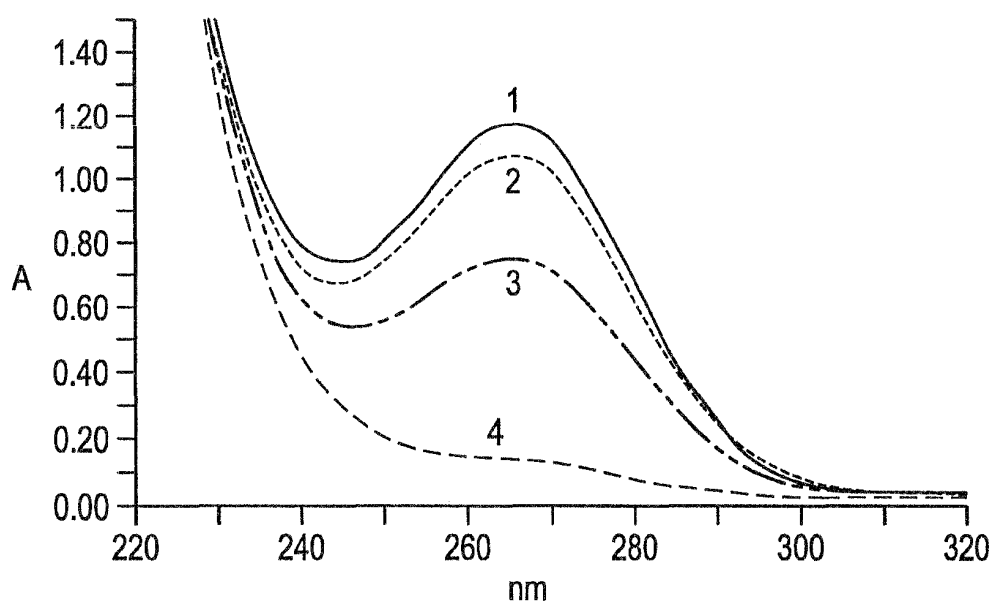
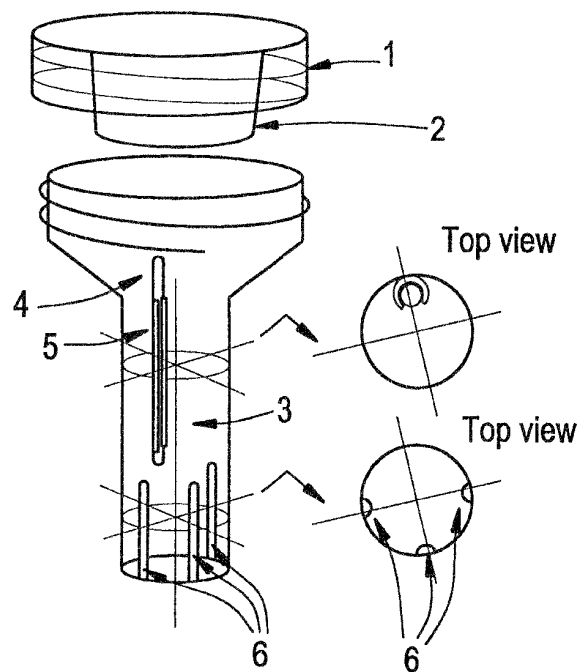


FIG. 10



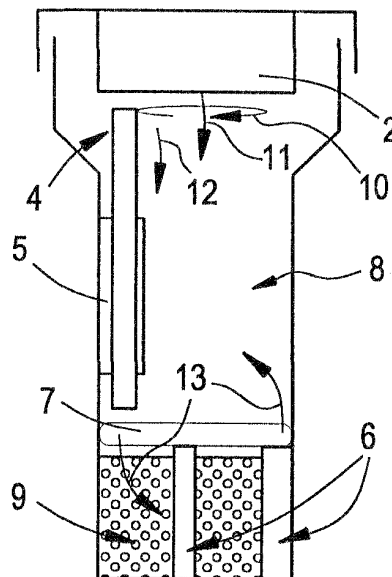
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FIG. 11



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COMPOSITIONS AND METHODS FOR OBTAINING NUCLEIC ACIDS FROM SPUTUM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/549,344, filed Nov. 20, 2014, which is a continuation of U.S. patent application Ser. No. 12/338,873, filed Dec. 18, 2008, which is a continuation of U.S. patent application Ser. No. 10/455,680, filed Jun. 5, 2003, now U.S. Pat. No. 7,482,116, which claims the benefit of U.S. Provisional Patent Application Ser. No. 60/386,397, filed Jun. 7, 2002, U.S. Provisional Patent Application Ser. No. 60/386,398, filed Jun. 7, 2002, and U.S. Provisional Patent Application Ser. No. 60/386,399, filed Jun. 7, 2002, each of which is hereby incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

The present invention relates to compositions and methods for preserving nucleic acids at room temperature for extended periods of time and for simplifying the isolation of nucleic acids.

DNA can be extracted from virtually every type of cell in the human body, with the exception of red blood cells. The usual source of bodily samples for extraction of DNA is venous blood, since the number of nucleated white blood cells (principally neutrophils and lymphocytes) is relatively high and quite consistent: the normal range is about 5 to 10 million white blood cells per milliliter of blood. The DNA content of human cells is about 6 micrograms per million cells, so 1 milliliter can theoretically yield from 30 to 60 micrograms of DNA. However, there are about 5 billion red blood cells per milliliter of blood, which, since they contain no DNA, must be removed to obtain pure DNA. Furthermore, the use of blood as a source of DNA has many other disadvantages. Collection of blood is not a trivial procedure. Taking of venous blood requires trained personnel. It is an invasive procedure, which frequently causes some distress and pain to the donor. Precautions are needed to minimize exposure of personnel to blood-borne pathogens. Once collected, the blood sample must be either frozen or quickly transported to a laboratory for extraction of DNA. For these reasons, venous blood is not the ideal source of DNA. A simpler procedure for obtaining blood is to collect a few drops after a finger prick and blotting it onto a piece of filter paper. Less training of personnel is required. Once dried, the DNA is quite stable. The amount of DNA recovered is small but sufficient for many forensic purposes. However, a finger prick is still an invasive procedure and heme derived from hemoglobin in blood can inhibit some types of DNA analysis.

Swabbing the inside of the cheek with a brush (a buccal swab) is another source of cells that contain DNA. It is much less invasive than taking of blood and can be collected by individuals with less training than is required in the collection of blood. Once collected, the time that useable DNA can be recovered can be extended by either drying the swab or wiping onto filter paper and drying it. However, as the inside of the mouth is not a sterile source (as compared to blood) and microbes can degrade the quality of the DNA after a period of time. The number of cells recovered by this procedure is not large and typically less than 1-2 micrograms of DNA can be expected in the entire sample.

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Saliva is a fairly clear, colorless fluid secreted principally by the major salivary glands (parotid, submandibular, and sublingual). Its function is to lubricate and cleanse the oral cavity, as well as to initiate the process of digestion. The parotid gland primarily secretes serous (watery) saliva, while the other glands secrete a mixture of serous and mucinous (sticky) saliva. Components of saliva include albumin, globulin, mucins, and digestive enzymes. It has long been known that cellular DNA is present in saliva and that this DNA is suitable for forensic purposes. Forensic use is typically limited to victim or suspect identification, using the tiny amounts of DNA from saliva that may be recovered at a crime scene or from the back of a postage stamp. The notion that saliva may be a reliable source of genomic DNA and a rival to venous blood samples for this purpose has been investigated more recently in a scientific publication (van Schie, et al., *J. Immunol. Methods* 208:91-101, 1997). The authors used freshly collected or frozen saliva samples and purified the DNA by a fairly complex extraction procedure. Estimates of the quantity of DNA recovered were based upon light absorption at 260 nm, a procedure known to be an unreliable method since other common biological macromolecules, such as RNA, have essentially the same ultraviolet light absorption spectrum. Nevertheless, these authors showed that quality genomic DNA was indeed present by gel electrophoretic analysis and polymerase chain reaction analysis for certain allelic polymorphisms. Another communication (Terasaki, et al., *Hum. Immunol.* 59:597-598, 1998) reported similar results about the suitability of saliva as a source of DNA for HLA typing by polymerase chain reaction analysis. Although the amount of DNA recovered was reported, the method used to measure DNA was not. These authors provided 3 examples where saliva dried on filter paper yielded DNA suitable for analysis.

With the increasing use of DNA-based analysis in forensics, law enforcement, military, human medicine, veterinary medicine, and research, there is a need for a product that would allow saliva to become a standard reliable source of DNA from an individual (to replace blood, the current standard). In forensic, military and mass disaster situations, for example, DNA samples are now routinely taken from living persons thought to be relatives of unidentified victims of accident or foul play, to aid in identification of the dead. Military personnel or other individuals who expect to encounter hazardous situations where their lives may be at risk may wish to store DNA samples prior to exposing themselves to these hazards. In the law enforcement area, convicted felons in both Canada and the United States are now required to provide DNA samples. DNA-based tests are expected to increase in medicine, such as testing for cystic fibrosis, cytochrome P450 isotypes, polymorphisms affecting susceptibility to infectious and autoimmune diseases, HLA typing, paternity issues, to name but a few. In clinical studies, an example would be to screen populations for colon cancer-predisposing genes or family members of a breast cancer victim for breast cancer predisposing genes. In all of these cases, there are significant advantages to providing a saliva sample rather than providing a blood sample as a source of DNA. All donors would prefer donating saliva rather than blood because of the discomfort, pain, or apprehension associated with phlebotomy or pin-pricks. Saliva has a further advantage of not requiring specialized personnel thereby reducing cost where mass sample collection is being carried out. The risk of blood-borne infection is likewise decreased.

In addition to the problem of developing a standard collection and preservation method for DNA in saliva, there

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remains an ongoing need to improve methods of overcoming problems specific to the recovery of nucleic acids from saliva. The problem of extraction of high molecular weight DNA and RNA from mammalian cells has been partially addressed by Bimboim in *Methods of Enzymology* 216:154-160, 1993, but this work was not extended to the recovery of nucleic acids from mucin-containing bodily fluids.

Multimeric proteins called mucins are high molecular weight glycosylated proteins that form a major part of a protective biofilm on the surface of epithelial cells, where they can provide a barrier to particulate matter and bind microorganisms. These glycoproteins contribute greatly to the viscoelastic nature of saliva. The major high-molecular-weight mucin in salivary secretions is MUC5B, one of four gel-forming mucins that exist as multimeric proteins with molecular weights greater than 20-40 million daltons. MUC5B is a large oligomeric mucin composed of disulfide-linked subunits.

It is known that reagents that reduce disulfides also reduce the viscosity of mucin, such as that found in sputum or saliva. Reducing agents, in particular sulfur-containing chemicals such as β -mercaptoethanol and dithiothreitol, are widely used in biochemistry. However, many biochemically relevant reducing agents are capable of reacting in solution with dissolved oxygen. This is known as autooxidation (also called autoxidation or autooxidation), where 1-electron reduction intermediates of oxygen are formed, viz., superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH). In addition, transitional metal cations function as catalysts and O_2^- has been demonstrated to be an intermediate. Unfortunately, reducing agents and reducing compositions of the prior art have a relatively short shelf life, especially in basic solutions, and stock solutions that contain reducing agents cannot be prepared and stored under ambient conditions for an extended period time, usually not more than a day or two.

Therefore, in addition to a need for a means to collect sputum or saliva, and subsequently preserving the nucleic acids contained therein by contacting them with a stabilizing composition, there is a need for the inclusion of a stable reducing agent into the composition, such that nucleic acids can be conveniently recovered from it, especially after extended periods of time in the presence of oxygen at neutral or mildly alkaline pH.

SUMMARY OF THE INVENTION

The present inventor has developed a composition, which, when mixed with a mucin-containing bodily fluid, preserves the nucleic acids at room temperature under ambient conditions for extended periods of time. There is no requirement for freezing of the samples before nucleic acid recovery and purification. The properties of this composition are that it (a) chemically stabilizes nucleic acids, (b) inhibits nucleases that may be present in the saliva, and (c) is compatible with proteolytic enzymes and other reagents used to purify/amplify oligo- or polynucleotides. A fourth and novel property of this composition is that it contains an agent that rapidly reduces the viscous properties of mucin, greatly facilitating the extraction of nucleic acids contained within.

Accordingly, a first aspect of the invention features a composition for preserving nucleic acids that includes a chelating agent, and a denaturing agent, where the pH of the composition is greater than 5.0. In one embodiment, the composition is an aqueous solution.

In another embodiment, the composition also includes a reducing agent. For example, it can include one or more of

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the following: ascorbic acid, dithionite, erythiorbate, N-acetylcysteine, cysteine, glutathione, dithiothreitol, 2-mercaptoethanol, dierythritol, a resin-supported thiol, a resin-supported phosphine, vitamin E, and trolox, or salts thereof. Desirably, the reducing agent is ascorbic acid, erythiorbate, N-acetylcysteine, dithiothreitol, or 2-mercaptoethanol, and most desirably, the reducing agent is ascorbic acid. In another embodiment, the composition does not contain ascorbic acid. In yet another embodiment, the concentration of the reducing agent in the composition is greater than or equal to 50 millimolar.

Antioxidant free-radical scavengers are also desirable reducing agents for the composition of the present invention. Examples include antioxidant vitamins, antioxidant hormones, antioxidant enzymes, thiols, and phenols.

Desirably, the reducing agent retains reducing activity for at least 46 days in the presence of one or more of the following: oxygen, ambient air, ambient light, and alkaline pH.

The chelating agent of the composition can be selected from the group consisting of: ethylenediamine tetraacetic acid (EDTA), cyclohexane diaminetetraacetate (CDTA), diethylenetriamine pentaacetic acid (DTPA), tetraazacyclododecanetetraacetic acid (DOTA), tetraazacyclotetradecanetetraacetic acid (TETA), and desferrioximine, or chelator analogs thereof. Desirably, the chelating agent is cyclohexane diaminetetraacetate (CDTA), diethylenetriamine pentaacetic acid (DTPA), tetraazacyclododecanetetraacetic acid (DOTA), or desferrioximine, and most desirably, the chelating agent is cyclohexane diaminetetraacetate (CDTA).

In another embodiment, the chelating agent of the composition inhibits metal redox cycling. By "inhibits metal redox cycling" is meant the inhibition of metal-based oxidation/reduction cycles that produce reactive oxygen free-radical species. Examples of redox ion pairs involved in such cycles include Fe^{2+}/Fe^{3+} , Cu^{1+}/Cu^{2+} , and various oxidation states of molybdenum, vanadium, nickel, and cobalt. Chelators that bind one or both ions of a redox ion pair can inhibit the production of reactive oxygen species such as, for example, hydroxyl radical (HO \cdot), hydroperoxyl radical (HOO \cdot), superoxide radical ($O_2^{\cdot-}$), nitric oxide radical (NO \cdot), or peroxyxynitrite radical (ONO $_2^{\cdot-}$).

The nucleic acid to be preserved by the composition can be DNA or RNA, including mRNA or viral RNA.

The pH of the composition can be between from about 5.0 and about 11.0, desirably from about 6.5 to about 7.5, and most desirably, about 7.0. For the preservation of DNA, a pH from about 7.0 to about 10.0 can be used. Depending on other components of the compositions, desirable pHs are about 7.5, about 8.0, or a pH range from about 8.0 to about 9.0. A buffer, such as HEPES, TRIS, or carbonate buffer can be added to the composition to maintain the pH in a constant range. For the preservation of RNA, a pH from about 5.0 to about 7.0, desirably from about 6.5 to about 6.8 can be used. Again, a buffer, such as BES, can be used to maintain the pH in a constant range.

The denaturing agent of the composition can be selected from the group consisting of: urea, dodecyl sulfate, guanidinium chloride, guanidinium thiocyanate, perchlorate, and an alcohol. Desirably, the denaturing agent is urea, dodecyl sulfate, or an alcohol, wherein the alcohol is 10%-60% of the total composition volume. The alcohols can be methanol, ethanol, n-propanol, isopropanol, n-butanol, trifluoroethanol, phenol, or 2,6-di-tert-butyl-4-methylphenol.

In another embodiment, the composition includes an antimicrobial agent. By "antimicrobial agent" is meant a

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substance or group of substances which reduces the rate of growth of an organism compared to the rate of growth of the organism in their absence. A reduction in the rate of growth of an organism may be by at least 5%, more desirably, by at least 10%, even more desirably, by at least 20%, 50%, or 75%, and most desirably, by 90% or more. The definition also extends to substances which affect the viability, virulence, or pathogenicity of an organism. An antimicrobial agent can be natural (e.g., derived from bacteria), synthetic, or recombinant. An antimicrobial agent can be bacteriostatic, bactericidal or both. An antimicrobial agent is bacteriostatic if it inhibits cell division without affecting the viability of the inhibited cell. An antimicrobial agent is bactericidal if it causes cell death. Cell death is commonly detected by the absence of cell growth in liquid growth medium (e.g., absence of turbidity) or on a solid surface (e.g., absence of colony formation on agar). Those of skill in the art know that a substance or group of substances which is bacteriostatic at a given concentration may be bactericidal at a higher concentration. Certain bacteriostatic substances are not bactericidal at any concentration. Desirably, the composition of the invention includes an alcohol as an antimicrobial agent, and most desirably the composition includes ethanol.

In another embodiment, the composition also includes an inhibitor of ribonuclease. Desirable inhibitors are selected from the group consisting of: heparin, heparan sulfate, oligo(vinylsulfonic acid), poly(vinylsulfonic acid), oligo(vinylphosphonic acid), and poly(vinylsulfuric acid), or salts thereof. The inclusion of an inhibitor of ribonuclease in the composition of the invention is particularly desirable when the nucleic acid to be preserved is RNA, desirably mRNA, or when the nucleic acid to be preserved is from a virus or a bacterium.

A second aspect of the invention features a method of reducing the viscosity of a mucin-containing bodily fluid or tissue by reducing disulfide bonds inherent to mucin, wherein the bodily fluid or tissue is mixed with a composition of the invention that includes a reducing agent. In one embodiment, the bodily fluid is sputum, desirably saliva. By "sputum" is meant that mucoid matter contained in or discharged from the nasal or buccal cavity of an animal, including saliva and discharges from the respiratory passages, including the lungs. In another embodiment, the method includes the recovery of a nucleic acid.

A third aspect of the invention features a method of preserving a nucleic acid contained in sputum that includes the steps of obtaining sputum from a subject, and contacting the sputum with a composition of the invention, thus preserving the nucleic acid.

In one embodiment, when the nucleic acid is DNA, the DNA is stable for more than 14 days, desirably more than 30 days, and more desirably more than 60 days. In another embodiment, when the nucleic acid is DNA and the composition does not contain ascorbic acid, the DNA is stable for more than 60 days, and desirably more than 360 days.

A fourth aspect of the invention features a method of recovering a nucleic acid from sputum that includes the steps of: i) obtaining sputum from a subject, ii) contacting the sputum with a composition of the invention to form a mixture, iii) contacting the mixture with a protease, and iv) recovering the nucleic acid from the mixture. Desirably, the protease is proteinase K or pronase.

In one embodiment of any of the second, third, or fourth aspects, the sputum is saliva. In another embodiment, the sputum is from a mammal, desirably a human. In yet another embodiment, the nucleic acid is DNA or RNA. If the nucleic

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acid is RNA, desirably it is mRNA or viral RNA. The nucleic acid can be from a source foreign to the subject from which the sputum sample is taken. For example, the nucleic acid can be from a bacterium or a virus that is residing in the buccal, nasal, or respiratory passages of the subject.

In a fifth aspect, the invention features a method of preserving and/or recovering a nucleic acid from a bodily fluid that includes, placing the bodily fluid into a first region of a container, placing a composition of the invention into a second region of the container, which is separated from the first region by a barrier, closing the container, and disturbing the integrity of the barrier such that the composition and the bodily fluid are brought into contact.

In one embodiment, the disestablishment of the barrier is coupled to the closing of the container when a lid is placed on it. In one example, the barrier is punctured. In a desirable example, the barrier is in the form of a pivoting sealing disc. In this example, attachment of the lid to the container forces the disc to pivot from its original position of spanning the space between the first region and the second region to a position in which both regions are exposed to each other, thereby forming a mixture between a composition of the invention and the bodily fluid is allowed. Desirably, the bodily fluid is sputum, and most desirably, saliva.

In a sixth aspect, the invention features a device for preserving and/or isolating a nucleic acid obtained from a biological sample. The device includes: a container that has a first region for collecting a biological sample and a second region containing a composition for preserving a nucleic acid, a barrier between the first region the second region that keeps the biological sample and the composition separate, a means for closing the container, and a means for disturbing the integrity of the barrier such that the composition is capable of contacting the biological sample. The first region can have an opening of from 2.0 to 7.0 cm, desirably from 2.5 to 3.5 cm, and most desirably 3.0 cm. Desirably, the biological sample is sputum, and most desirably, saliva.

In one embodiment of the sixth aspect, the nucleic acid-preserving composition is a composition of the present invention. In another embodiment, the means for closing the container is coupled to the means for disturbing the integrity of the barrier. In yet another embodiment, the means for closing the container is an airtight lid.

In a seventh aspect, the invention features a method of manufacturing a device for preserving a nucleic acid in a biological sample that includes: providing a container that has a first region and a second region, with the first region suitable for containing a composition of the invention and the second region having an opening suitable for the application of a biological sample; placing the composition into the first region; and applying a barrier to the container between the first region and the second region, with the barrier being impermeable to the composition and capable of being disestablished.

In an embodiment of either the sixth or seventh aspect, the barrier can be a pivoting disc, where in a first position, the disc spans the compartment and separates the first and second areas. Pivoting the disc to a second position (e.g., by connecting a screw-on lid to a plunger mechanism which contacts the disc, causing it to pivot when the lid is screwed on) disestablishes the barrier and allows the biological sample contained in the first region to contact the composition that is contained in the second region.

By "about" is meant +/-10% of the stated value or a chemical or obvious equivalent thereof.

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By "alcohol" is meant a water-miscible organic compound containing a hydroxyl group, including water-miscible mixtures of hydroxyl-containing organic compounds.

By "antioxidant free-radical scavenger" is meant a substance that reduces a reactive oxygen free radical species. Such free radicals include, for example, hydroxyl radical (HO \cdot), hydroperoxyl radical (HOO \cdot), superoxide radical (O $_2^{\cdot-}$), nitric oxide radical (NO \cdot), or peroxyxynitrite radical (ONOO $^{\cdot-}$).

By "aqueous solution" is meant a solution or suspension that contains 30% or more water by volume.

By "bodily fluid" is meant a naturally occurring fluid from an animal, such as saliva, serum, plasma, blood, urine, mucus, gastric juices, pancreatic juices, semen, products of lactation or menstration, tears, or lymph.

By "biological sample" is meant any sample containing nucleic acids that has been obtained from or deposited by an animal. Non-limiting examples include skin, hair, bodily fluids, fecal matter, and tissue.

By "chelator analog" is meant a derivative chelator compound with the same backbone structure and having the same general properties as the parent chelator compound.

By "denaturing agent" is meant a substance that alters the natural state of that to which it is added.

By "mucin" is meant any mucoprotein that raises the viscosity of the medium surrounding the cells that secrete it.

By "mucoïd" is meant any bodily fluid containing mucin.

By "nucleic acid" is meant a chain of the nucleotides, including deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), typically found in chromosomes, mitochondria, ribosomes, bacteria, or viruses.

By "nucleic acid-preserving composition" is meant any composition of the present invention, unless otherwise specified.

When referring to a nucleic acid, by "stable" is meant that at least about 50% of the initial amount of high molecular weight nucleic acid (DNA, RNA, mRNA, or viral RNA) contained in a sample is still present after storing the sample at ambient temperature (i.e., 20° C. to 25° C.) for the specified time period. The amount of high molecular weight DNA in a sample can be quantified by densitometry analysis of the high molecular weight DNA band from an agarose gel (see FIG. 1 and Example 4).

By "resin-supported phosphine" is meant a polymer that contains a multiplicity of covalently-bound phosphine groups.

By "resin-supported thiol" is meant a polymer that contains a multiplicity of covalently-bound sulfhydryl groups.

By "saliva" is meant the secretion, or combination of secretions, from any of the salivary glands, including the parotid, submaxillary, and sublingual glands, optionally mixed with the secretion from the buccal glands.

By "sputum" is meant that mucoid matter contained in or discharged from the nasal or buccal cavity of a mammal, including saliva and discharges from the respiratory passages, including the lungs.

By "subject" is meant any animal. Desirably, the subject is a mammal that can produce saliva for the purposes of nucleic acid extraction. Most desirably, the subject is a human.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications

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within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an electrophoresis agarose analysis of DNA isolated from saliva using the capacity of methods of one embodiment of the invention.

FIG. 2 is a graph illustrating real time PCR of stimulated saliva DNA of Example 5.

FIG. 3 is a graph illustrating real time PCR of unstimulated saliva DNA of Example 6.

FIG. 4 is an electrophoresis agarose analysis of the DNA in saliva samples mixed with compositions of the invention, the mixtures having been incubated for various times at various temperatures.

FIG. 5 shows structures of (oxidized) ascorbate anion, (reduced) dehydroascorbic acid, and a free radical intermediate

FIG. 6 is a compilation of two spectrophotometric scans of sodium ascorbate (100 μ M) in CB (1 mM CDTA, 10 mM. BES, pH 7.4), prepared under aerobic conditions over 30 minutes at room temperature (scan 1) and 3 minutes after addition of a few crystals of MnCl $_2$. (scan 2), as per Example 8.

FIG. 7 is a compilation of spectrophotometric scans, at the indicated times, of the 100 μ M sodium ascorbate prepared in CB of Example 8. The solution was exposed to ambient atmosphere and temperature between scans but was not contacted with MnCl $_2$ (see Example 9).

FIG. 8 is a graph of absorbances at 265 nm, obtained at the indicated times, of a solution of sodium ascorbate (250 mM) containing 30 mM Tris-HCl, pH 8.0, 30% ethanol, 3 mM CDTA, mixed with 50 mL of CB, as per Example 10. The stock solution was maintained at room temperature and no precaution was taken to exclude ambient atmosphere or ambient light.

FIG. 9 is a compilation of spectrophotometric scans of the 46 day-old solution prepared in Example 10. Scan 1 (t=46 days) was taken before the addition of MnCl $_2$. Scan 2 was taken 2 minutes after the addition MnCl $_2$. Scan 3 was taken 8 minutes after the addition MnCl $_2$. Scan 4 was taken 27 minutes after the addition MnCl $_2$.

FIG. 10 is an exploded view of a sample container of the invention. Included in the figure is a cross-sectional top view taken at line 1-1 of container 3 showing plunger 4 and plunger channel 5. Also shown is a cross-sectional top view taken at line 2-2 of container 3, showing supports 6 for sealing disc 7 (not shown in this figure but shown in FIG. 11).

FIG. 11 is a side view of the sample container of FIG. 10, now showing sealing disc 7.

DETAILED DESCRIPTION

The following standard abbreviations are used herein: DNA, deoxyribonucleic acid; RNA, ribonucleic acid; mRNA, messenger RNA; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; BES, N,N-bis[2-hydroxyethyl]-2-aminoethane-sulfonic acid; TRIS, tris(hydroxymethyl)aminomethane, CDTA, cyclohexane diaminetetraacetate; DTPA, N,N-bis(2-(bis(carboxymethyl)amino)ethyl)glycine; DOTA, 1,4,7,10-tetraazacyclododecanetetraacetic acid; and TETA, 1,4,8,11-tetraazacyclotetradecanetetraacetic acid.

Compositions of the Invention

The present inventors have developed compositions that render sputum as a viable option to the use of blood as a source of nucleic acids. The compositions provide the advantageous properties of chemical stabilization of nucleic acids and the inhibition of nucleases, including deoxyribo-
nucleases, and microbial growth. Chemical stabilization of the nucleic acids in a saliva sample is achieved through the use of buffers to maintain an appropriate pH, as well as the use of chelating agents to prevent the phenomenon of metal redox cycling or the binding of metal ions to the phosphate backbone of nucleic acids. The chelating agents of the invention also participate in the inhibition of deoxyribonucleases and microbial growth, which can be additionally inhibited by the inclusion of denaturing agents and/or other suitable antimicrobial substances, such as ethanol, into the compositions of the invention. The compositions of the invention can also include one or more reducing agents, which can reduce sample viscosity, thereby making nucleic acid recovery an easier process.

Accordingly, the present invention features a composition for preserving and/or recovering nucleic acids from sputum, desirably saliva, that includes one or more chelators and one or more denaturing agents, wherein the pH of the composition is greater than 5, desirably within a pH range of about 6 to about 11, more desirably within a pH range of about 7.5 to about 10.0, and most desirably, within a pH of about 7.0.

The chemical backbone and the purine bases of DNA are most stable at slightly alkaline pH, with an optimal stability generally recognized as being within a pH range of about 7-11, and desirably a pH of about 8. Below a pH of about 6, depurination (i.e., spontaneous loss of purine bases from the deoxyribose-phosphate backbone) can occur. Above a pH of about 10, spontaneous loss of amino groups from cytosine nucleotides may occur, thereby converting cytosine to uracil. Above a pH of about 12, DNA is denatured, converting it from the double-strand form to the single-strand form. In contrast, RNA is most stable in the pH range of 5.0 to 7.0, desirably a pH of from 6.5 to 6.8. Accordingly, the pH of the composition may be adjusted using pH buffers, desirably those that best control the pH within the range of about 5 to about 11. Examples of pH buffers with desirable properties include, but not limited to, TRIS hydrochloride, HEPES and BES.

DNA has a strong affinity for metal ions, some of which, such as the common transition metals iron or copper, can catalyze the formation of reactive oxygen species. Therefore, a composition of the invention includes one or more chelators that can form complexes with metal ions to prevent them from binding to DNA, remove metal ions that have already bound to DNA, or bind to metal ions (e.g., Fe(II)/Fe(III) or Cu(I)/Cu(II)) strongly enough to inhibit their redox cycling, and hence, the formation of reactive oxygen species. EDTA, a commonly used chelator in biological reagents, can be of some use for either of these purposes. More desirable are stronger chelators (i.e., chelators with a higher dissociation constant than EDTA when bound to a metal), used alone or in combination, that include, but are not limited to, CDTA, DTPA, DOTA, TETA, and desferioximine, or chelator analogs thereof. The amount or concentration of chelator will depend upon the strength of the chelator, which would need to be determined empirically. For CDTA, concentrations in the 1-20 mM range are sufficient, however other concentrations would work, and the compositions of the invention are not intending to be limited to this range.

Deoxyribonucleases and ribonucleases are enzymes that breakdown DNA or RNA, respectively. Their main source in the digestive tract is secretions of the pancreas, although lower levels may be present in cells of the salivary gland and buccal mucosa. In addition, microorganisms resident in the mouth or from recently ingested foods may contain deoxyribonucleases or ribonucleases. Pancreatic deoxyribonuclease is known to require divalent metal ions such as Mg(II), Mn(II) and/or Ca(II) for enzymatic activity. The strong chelators described above, in addition to providing chemical stability to the nucleic acids, will inhibit this class of metal ion-requiring deoxyribonucleases. The action of deoxyribonucleases and ribonucleases can also be inhibited by denaturing agents that will destroy the complex structures of these enzymes (proteins). Hence, denaturing agents are included in the nucleic acid preserving composition of the invention. Examples of denaturing agents that may be used (alone or in combination) include, but not limited to, urea, soluble salts of dodecyl sulfate and other strong detergents, guanidinium chloride, guanidinium thiocyanate, soluble salts of perchlorate, alcohols, such as ethanol, above 10%. Other reagents, such as heparin, heparan sulfate, or oligo (vinylsulfonic acid) (Smith, et al., *J. Biol. Chem. Mar.* 20, 2003; [epub ahead of print]) are known to inhibit the action of deoxynucleases and/or ribonucleases.

Low specificity proteases such as proteinase K are frequently used in the purification of nucleic acids. Since proteases are themselves proteins, their action can be inhibited by denaturing agents. Thus, a balance must be struck between the concentration of denaturing agents that will, on the one hand, inhibit deoxyribonucleases or ribonucleases and denature other proteins in saliva and, on the other hand, not significantly inhibit the proteolytic enzymes. At later stages in DNA purification, the DNA is often concentrated by precipitation with alcohol. Thus, salts, buffers, chelators and other components of the nucleic acid preserving/recovery solution must be chosen so as not to precipitate when concentrations of alcohol over 50% are added to precipitate the DNA.

The viscosity of sputum and saliva depends upon the presence of very high molecular weight glycoproteins complexes called mucins, particular the gel-forming mucins (Offner, et al., *Adv. Dent. Res.* 14:69-75, 2000; Seregini, et al., *Tumori* 83:625-632, 1997). It has been found that the inclusion of a reducing agent into a composition of the invention has the effect of markedly reducing the viscosity of saliva, especially "unstimulated" saliva, thereby facilitating the recovery of nucleic acids. Accordingly, in one embodiment, a composition of the invention further includes one or more reducing agents. The reducing agents are desirably at high concentration (greater than 0.05 M). While not wishing to be limited by theory, it is presumed that the reducing agent reduces the viscosity of the saliva by breaking disulfide bonds that hold together chains of mucin, and that any reducing agent that has the appropriate redox potential to reduce disulfide bonds in proteins would be suitable. Desirably, the reducing agent is selected from the group consisting of: ascorbic acid, dithionite, erythorbate, N-acetylcysteine, cysteine, glutathione, dithiothreitol, 2-mercaptoethanol, dierythritol, a resin-supported thiol, a resin-supported phosphine, vitamin E, and trolox, or salts thereof.

In another embodiment, a composition of the invention that includes a reducing agent maintains reducing capacity at room temperature in a sealed container in the presence of ambient oxygen, and/or in the presence of ambient light for more than a week, desirably for up to about 46 days, and

most desirably for at least 46 days. This embodiment combines the nucleic acid stabilization provided by a strong chelator a denaturing agent, and a reducing agent in a composition with a pH within the range of about 6 to about 11, and desirably a pH of about 8.0.

A particularly desirable reducing agent is sodium ascorbate. As well as an important dietary antioxidant micronutrient, ascorbic acid (vitamin C) is a non-thiol reducing agent and is inexpensive, non-toxic, and stable in the presence of the chelators and denaturing agents that are included in the compositions of the invention. The structures of (oxidized) ascorbate anion, (reduced) dehydroascorbic acid, and a free radical intermediate are shown in FIG. 5. The most thoroughly studied oxidation reaction of ascorbate is its oxidation by oxygen. As with many other reducing agents, trace amounts of transitional metals such as iron or copper can promote autooxidation (Buettner, *Free Radic. Res. Commun.* 1:349-53, 1986; Buettner and Jurkiewicz *Radiat. Res.* 145:532-41, 1996; Miller, et al., *Free Radic. Biol. Med.* 8:95-108, 1990). Metal cation-catalyzed oxidation of ascorbate can be conveniently monitored as a decrease in absorbance at 265 nm (Buettner *Free Radic. Res. Commun.* 10:5-9, 1990), as described in Example 8 and shown in FIGS. 5, 6, and 8. Certain chelating agents can appreciably slow down autooxidation of ascorbate at pH 7.0 or lower (Buettner *J. Biochem. Biophys. Methods* 16:27-40, 1988), as described in Example 10 and shown in FIG. 8.

In another embodiment, a composition of the present invention includes one or more chelators, one or more denaturing agents, and one or more antimicrobial agents, wherein the pH of the composition is within a pH range of about 6.0 to about 11.0, desirably at a pH of about 8.0. Microbial growth may also be inhibited by the strong chelators and denaturing agents, for example, ethanol, described above. Therefore, in a further embodiment of the

Methods of the Invention

The present invention features methods of collecting, preserving, and recovering nucleic acids from sputum using a composition of the invention. The methods of the invention involve contacting a sputum sample from a subject with a composition of the invention and optionally mixing the resulting solution with a protease, such as pronase or proteinase K. Furthermore, some compositions of the invention feature a reducing agent that can facilitate the recovery of nucleic acids from composition/sample mixtures by decreasing the viscosity of these mixtures.

Accordingly, one aspect of the invention features a method of preserving a nucleic acid contained in sputum that includes the steps of obtaining sputum from a subject, and contacting the sputum with a composition of the invention, thus preserving the nucleic acid. Examples 1 and 2 describe the collection of saliva, both from subjects that can follow instructions and from those that can not.

The sputum is typically contacted with a composition of the invention upon collection or immediately after it is collected, and preferably not much later than about 1 hour after collection. This time can vary depending on storage conditions of the sputum after collection. For example, it could be indefinite if stored frozen or perhaps 1-2 days if stored at 4° C. A reducing agent can be in the preserving composition used, or added at a later time prior to nucleic acid isolation. Desirable reducing agent-containing compositions are those that are stable and retain a reducing capacity for more than a week, desirably for up to about 46 days, and most desirably for at least 46 days.

In an example (see Example 5), the results of which are presented in Table 1, saliva was collected and mixed with approximately an equal volume of a composition of the invention (see Example 3 for preparation), and analyzed for DNA content by PCR analysis at later timepoints.

TABLE 1

Estimated amounts of DNA in saliva samples*										
Donor #										
1	2	3	4	5	6	7	8	9	10	11
Stim. saliva collected on 02Feb26, analyzed 64 days by the DNase method										
21.2	21.4	16.6	16.0	28.8		44.8	22.2	16.6		
Unstim. saliva collected on 02Mar25, analyzed 15 days later by DNase method										
		64.2				80.6	24.4	27.2	69.0	

*DNA content in nanograms per microliter

present invention, a composition for preserving and/or recovering DNA from sputum includes one or more chelators and one or more denaturing agents, wherein at least one or more of the denaturing agents and/or chelating agents is present in amounts to act as an antimicrobial agent.

Reagents that indicate when a biological sample has been contacted with a composition of the invention can also be included as part of the composition. Desirable are those reagents that result in a visual color change of the composition solution upon mixing with the added sample. These reagents can function by reacting with any number of functional groups that are contained in biological samples, including, for example, amines, thiols, or glycosyl groups. Such colorimetric reagents are known to those skilled in the art and are chosen in such a manner that other components of the composition do not interfere with their effective usage.

To collect the sputum from the subject it is preferred that the mouth be rinsed before sampling. Food particles can introduce foreign DNA and saliva transferred by kissing can be a source of foreign human DNA. The mouth can be rinsed with about 50 mL of tepid water by vigorous swishing or by brushing with a tooth brush without tooth paste. Unstimulated saliva is usually of the mucinous type and is secreted at a slow rate. Stimulated saliva (anticipation of tasty food, sweet or sour candy) is of the serous (watery) type and secreted at a faster rate. It has been found (see Table 2) that there is more DNA in 2 mL of unstimulated saliva than 2 mL of stimulated saliva. After rinsing of the mouth and waiting about two or three minutes, the donor may spit a volume (for example, about 2 mL) of "unstimulated" saliva into the receiving tube. If this proves to be difficult, saliva flow can conveniently be stimulated with a cube of table sugar, or any other such saliva-stimulatory substance that does not interfere with DNA recovery or purification.

TABLE 2

Comparison of DNA content of unstimulated and stimulated saliva		
Donor #7	unstimulated	stimulated
Collected on 2002 Apr. 6, analyzed 2 days later by the DNase method	36.2*	21.8*

*Estimated amount of DNA in ng per μ L of original undiluted saliva sample

Another aspect of the invention features a method of reducing the viscosity of a mucin-containing bodily fluid or tissue by reducing disulfide bonds inherent to mucin, wherein the bodily fluid or tissue is mixed with a composition of the invention that includes a reducing agent. In one embodiment, the bodily fluid is sputum, desirably saliva.

Yet another aspect of the invention features a method of recovering a nucleic acid from sputum that includes the steps of: i) obtaining sputum from a subject, ii) contacting the sputum with a composition of the invention to form a mixture, iii) contacting the mixture with a protease, and iv) recovering the nucleic acid from the mixture.

Suitable proteases include, for example, proteinase K or pronase. The protease may suitably be in a dry form that would become activated once mixed with sputum and a composition of the invention. In one embodiment, the protease is deposited onto an interior surface of the collection device. This can be accomplished by dissolving the protease in a solution made up of equal volumes of 5% sucrose in water and 5% glycerol in ethanol and then, after placing the solution on the surface, removing the volatiles under a controlled vacuum to leave the protease bound to the surface as a sticky residue. If the composition does not contain a reducing agent (or even if it does), a reducing agent can be added at any time prior to isolation of the nucleic from the sample, desirably prior to or concurrently with contacting the sample with a suitable protease.

When sputum is mixed with a composition of the present invention, cells are disrupted, nucleic acids are liberated from the cells, membranous material is solubilized, proteins are stripped from the nucleic acids, and protein digestion begins. If present, a reducing agent in the composition reduces the viscosity of the gel-forming mucin. Incubation can be at room temperature over a relatively long period of time (days or weeks) while samples are being shipped to a laboratory for analysis. If transferred to a laboratory soon after collection, incubation at 55° C. for 4 to 16 hours is sufficient to allow the activated protease to digest the majority of protein to small peptides or amino acids. Under such conditions, nucleic acids and polysaccharides remain relatively intact.

Once digestion is complete, nucleic acid isolation can be performed using any technique known in the art (*Short Protocols in Molecular Biology*, 5th Edition Frederick M. Ausubel, Roger Brent, Robert E. Kingston, David D. Moore, J. G. Seidman, John A. Smith (Editor), Kevin Struhl (Editors). ISBN: 0-471-25092-9. 2002. John Wiley and Sons). In one example, in which SDS is used as a denaturant component of the composition, a "precipitation solution" consisting of, for example, potassium chloride may be added to a portion of the sputum-composition mixture resulting in the precipitation of potassium dodecyl sulfate, after standing on ice to cool the solution. Following a short period of centrifugation to remove the precipitate and any residual insoluble material, the supernatant is collected. At this stage, the supernatant is expected to contain as much as 10-30

nanograms per microliter of DNA. For analyses where as little as 1 nanogram of DNA is sufficient, the sample can be diluted.

When larger amounts of DNA are required, the DNA in the supernatant can be precipitated by the addition of alcohol and redissolved in any suitable buffer. This step has the effect of removing inhibitory components of the composition, which are present to preserve the nucleic acids during transport to the laboratory.

If more highly purified DNA is required, then other known purification steps can be used (*Short Protocols in Molecular Biology*, 5th Edition Frederick M. Ausubel, Roger Brent, Robert E. Kingston, David D. Moore, J. G. Seidman, John A. Smith (Editor), Kevin Struhl (Editors). ISBN: 0-471-25092-9. 2002. John Wiley and Sons), such as extraction with phenol or solid-phase extraction. It should be noted that, because the DNA is in a relatively pure state using the procedures described above, any additional purification steps are made easier when compared to analogous purifications of DNA originating from a blood sample.

The methods of the present invention can be used to isolate nucleic acids from sputum for any application requiring a nucleic acid sample. For example, some specific applications of the methods of the present invention include, but are not limited to, forensic applications, medical applications (including genetic screening and disease typing), and paternity testing.

Another aspect of the invention features a method of preserving and/or recovering a nucleic acid from a bodily fluid that includes, placing the bodily fluid into a first region of a container, placing a composition of the invention into a second region of the container, which is separated from the first region by a barrier, closing the container, and disturbing the integrity of the barrier such that the composition and the bodily fluid are brought into contact. Collection devices of the invention, which also can serve as containers for bring the compositions and nucleic acid-containing bodily fluids together are described below.

Collection Devices

The invention also provides a novel collection device useful for collecting a biological sample from a subject, and subsequently mixing the collected sample with a composition intended to stabilize, preserve, or facilitate the recovery of components of the sample. Such components may include, without limiting the invention, nucleic acids, proteins, peptides, toxins, chitins, fatty acids, and glycogens. Non-limiting examples of biological samples are skin, hair, fecal matter, bodily fluids, and tissue.

Desirably, the invention features a device for preserving and/or recovering a nucleic acid obtained from a biological sample. The device includes: a container that has a first region for collecting a biological sample and a second region containing a composition for preserving a nucleic acid, a barrier between a first region and a second region that keeps the sample and composition separate, a means for closing the container, and a means for disturbing the integrity of the barrier, such that the composition is capable of contacting the bodily sample. In one embodiment, the composition is a composition of the present invention. In another embodiment, the sample is a biological fluid.

The collection device of the invention simultaneously serves several functions. Some of the desirable features of this collection vessel include one or more of the following:

a) it may be constructed of a sturdy breakage-resistant plastic, desirably a biocompatible plastic. Desirably, the container would be constructed from a material that would not leach chemicals into the container's contents;

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b) it would have a broad mouth that would make it relatively simple for a subject to place the required volume of fluid sample, desirably expectorated sputum, and most desirably expectorated saliva, into the device's container;

c) the bottom part of the container would be narrow to reduce the overall volume of the container to make it easier to collect the small volume (1-2 milliliters) of fluid that would be expected from a routine sampling, in particular, when the sample is an expectorate. Optionally, the device would contain markings to allow for an estimate of the sample volume collected;

d) the means for closing the container may be a cap that is designed to lock once tightened to become tamper-resistant;

e) the means for closing the container may be a cap that is designed to provide a liquid-tight and/or airtight seal for the container once the cap is fixed into place;

f) the barrier may be a septum or plastic bag compact lent that would separate the composition from the fluid until the septum or bag compartment is pierced or the contents otherwise released;

g) the barrier may be in the form of a pivoting partition. In this embodiment, attachment of the lid to the container forces the partition to pivot from its original position of spanning the space between the first region and the second region to a position in which both regions are exposed to each other and contact between the composition contained in one space and the bodily fluid contained in the other space is allowed;

h) the barrier can be press fit, glued, or heat fit into place;

i) the means for closing the container may be coupled to the disestablishment of the barrier; and

j) an antimicrobial agent that coats the outside of the device.

A device of the invention is shown in FIGS. 10 and 11. With cap 1 not attached to the device, a biological sample (not shown) is applied to a first region 8 of container 3, which is separated from a second region 9 by sealing disc 7. After sample application, cap 1 is placed onto the device and secured via a screw thread mechanism to a tight fit, thereby sealing container 3. As the cap is twisted on (shown by dotted line and arrow 10, ram 2, which is attached to cap 1, moves downward as shown by dotted line arrow 11. This downward movement forces plunger 4, which is contained in plunger barrel 5, downward as indicated by dotted line and arrow 12. The downward movement of plunger 4 forces sealing disc 7 to pivot, as shown by dotted line and arrow 13. Pivoting of disc 7 disestablishes the barrier between regions 8 and 9, thereby permitting contact between the sample and a composition of the invention, shown as a dotted solution contained in region 9.

Kits

The present invention also features kits for performing the methods of the invention that include a device of the invention containing a composition of the invention, with instructions for stabilizing, preserving, or facilitating the recovery of nucleic acids from a biological sample by using the device to bring a biological sample into contact with the composition.

EXAMPLES

Example 1

Protocol for Obtaining Saliva Samples from Subjects Capable of Following Instructions

The subject is instructed to wait for a period of 20-30 minutes before last eating. The subject will brush his teeth

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without using toothpaste, if possible. The subject will rinse his mouth vigorously with 50 mL of cool or tepid water. The subject will then spit saliva into the special collection tube until the level of saliva reaches the 2 mL mark. This may take several minutes. If the subject finds that he is unable to deliver sufficient saliva, he will be given a cube of table sugar to chew, and told not to be concerned if some of the sugar is spit into the tube.

When the required amount of saliva is collected, it is mixed with 2 mL of a nucleic acid-preserving composition. The precise way this will be introduced will depend upon the container design.

Once the composition is introduced, the cap is attached to the container and tightened to seal it securely. The container is then vigorously shaken and the process is complete. The DNA is now in an intermediate preserved state. It can be maintained in a frozen state or at any temperature up to about 60° C.

The container can be mailed back to the testing lab at room temperature.

Example 2

Protocol for Obtaining Saliva Samples from Babies, Very Young Children and Infirm Adults Incapable of Following Instructions

A rubber or plastic tube or nipple will be introduced into the mouth, attached to a sponge, suction bulb or small syringe, and kept in the mouth for several minutes until visible drooling occurs. A bit of sugar cube will be placed in the mouth to stimulate saliva if necessary. The responsible adult will wear disposable gloves provided for the purpose to avoid contamination with his/her DNA. The responsible adult will draw saliva into the bulb or syringe and transfer it into the collection container. The DNA preserving/extraction composition is introduced and the container is capped and sealed. The tube is vigorously shaken for 1 minute.

Example 3

Preparation of a Nucleic Acid-Preserving Composition

The composition of the nucleic acid-preserving solution used in Examples 4-6 is 33 mM TRIS-HCl, 0.67 M urea, 0.67 M LiCl, 0.6% sodium dodecyl sulfate, 3.3 mM CDTA, 30% ethanol, and 0.25 M sodium ascorbate, all adjusted to a final pH of 8.0. In the examples, the composition is mixed with an equal volume of saliva. Subsequent to these experiments, it has been found that a composition which is 0.3 M TRIS-HCl, 0.67 M urea, 0.67 M NaOAc, 0.6% sodium dodecyl sulfate, 3.3 mM CDTA, 30% ethanol, and 0.1 M sodium ascorbate, all adjusted to a final pH of 8.0, stabilizes DNA for longer periods of time.

Example 4

Extraction of Minimally Purified Chromosomal DNA from the Stimulated Saliva of 8 Different Donors

After collection of saliva in an equal volume of the composition as noted in Example 3, followed by 14 days storage at room temperature, a 0.25 mL portion of each donor's sample was treated with proteinase K, centrifuged briefly to remove insoluble material and the DNA therein

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was precipitated with 2 volumes of ethanol. The precipitate was dissolved in 0.05 mL of water, and an 8 μ L aliquot (equivalent to about 20 μ L of undiluted saliva) was analyzed by electrophoresis on a 0.8% agarose gel, stained with ethidium bromide to visualize the DNA (see FIG. 1). Of note is the characteristic band of chromosomal DNA present in all samples at the position of the arrow, that corresponds to the position of chromosomal DNA extracted from white blood cells (data not shown).

Example 5

“Real Time” Polymerase Chain Reaction Using
DNA from Stimulated Saliva

Stimulated saliva samples collected on 26 Feb. 2002 (see Table 1) and stored at room temperature were analyzed 62 days later. Minimally purified DNA was prepared as follows: an aliquot was centrifuged to remove insoluble material; to the clarified supernatant was added 2 volumes of ethanol; the precipitate containing DNA was collected by

centrifugation and redissolved in water. A volume of the redissolved DNA equivalent to 0.05 microliters of each of the original saliva samples was used for analysis. Real time PCR was carried out using a Roche Light Cycler instrument, where the fluorescent dye SYBR green I was added to follow the reaction (see results of FIG. 2). The primers were designed to detect the human Clotting Factor IX gene (Grant, et al., *J. Immunol. Methods* 225:61-6, 1999). C=control, highly purified white blood cell DNA. Each curve represents results using saliva DNA from different donors, represented by a number. These results using real time PCR demonstrate the suitability of minimally purified saliva DNA from different donors for PCR analysis.

Example 6

“Real Time” Polymerase Chain Reaction Using
DNA from Unstimulated Saliva

FIG. 3 is a graph showing saliva DNA samples collected on 2002 Mar. 25 (see Table 1) and analyzed on 30 days later in accordance with FIG. 1. Minimally purified DNA was used Polymerase chain reaction and other conditions as described in Examples 4 and 5 except saliva collection was done under unstimulated conditions. Numbers refer to individual donors. C is control DNA, a highly purified sample of DNA purified from blood.

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Tables 1 and 2 show estimates of DNA recovered from saliva samples. In all cases, the individual donor has been identified by a unique number. These data show that the amount of DNA that can be recovered from this group of donors ranges from 16 micrograms per milliliter of saliva and higher. Estimation of the amount of DNA by chemical methods such as DABA presents some problems and the DNase method provides most reliable results.

Example 7

Stability Studies on DNA from Saliva

Saliva was mixed with an equal volume of the indicated composition and the mixture was incubated for the indicated time period at the indicated temperature (see Table 3). After incubation, approximately 40 μ L of mixture was digested briefly with ribonuclease to remove the majority of the RNA present in the sample, then applied to the indicated lane of a 0.8% agarose gel. Following electrophoresis, the gel was stained with ethidium bromide as in Example 4.

TABLE 3

Lane No.	Composition	Incubation Conditions
1	0.5M NaOAc, 0.2M TRIS-HCl, 0.15M Na ascorbate, 10 mM CDTA, 1% SDS, 30% (v/v) ethanol, pH = 9.5	70° C. for 3 days, then 50° C. for 16 days
2	0.5M NaOAc, 0.2M TRIS-HCl, 10 mM CDTA, 1% SDS, 30% (v/v) ethanol, pH = 9.5	50° C. for 21 days
3	0.5M NaOAc, 0.2M TRIS-HCl, 10 mM CDTA, 1% SDS, 30% (v/v) ethanol, pH = 9.5	70° C. for 3 days, then 50° C. for 31 days
4	0.67M LiCl, 33 mM TRIS-HCl, 0.67M urea, 0.6% SDS, 3.3 mM CDTA, 30% (v/v) ethanol, pH = 8.0	20° C.-25° C. for 15 months
5	0.67M LiCl, 33 mM TRIS-HCl, 0.67M urea, 0.6% SDS, 3.3 mM CDTA, 30% (v/v) ethanol, pH = 8.0	20° C.-25° C. for 15 months
6	Control chromosomal DNA prepared from white blood cells	

Example 8

Rapid Autooxidation of Ascorbate in the Presence
of a Transition Metal Ion

A solution of sodium ascorbate (100 μ M) in CB (10 mM BES, pH 7.4, containing 1 mM CDTA) was freshly prepared under aerobic (equilibrated with ambient air) conditions. Several spectrophotometric scans over 30 minutes at room temperature showed no change in the absorbance profile (all similar to scan (1)). Scan (2) was taken 3 minutes after addition of a few crystals of $MnCl_2$. The results can be seen in FIG. 6. As shown, 100 μ M ascorbate at neutral pH has an absorbance (λ_{max} =265 nm) of about 1.25 (corresponding to the expected molar extinction coefficient (A_M) of about 12,500. Upon addition, the transition metal, manganous chloride, catalyzed the autooxidation of ascorbate, which can conveniently be monitored by a decrease in absorbance at λ =265 nm (Buettner, *Free Radic. Res. Commun.* 10:5-9, 1990).

Example 9

Spontaneous Autooxidation of Ascorbate

Repeated scans at the indicated time points were taken of an aliquot of the 100 μ M sodium ascorbate solution prepared

in Example 8, before the addition of $MnCl_2$. The sample was exposed to air and maintained at room temperature between scans. The results are illustrated in FIG. 7, and indicate that autooxidation of ascorbate occurs at pH 7.4 can occur over an extended period of time in the presence of low concentrations (1 mM) of CDTA, a “strong” chelator.

Example 10

Stability of Sodium Ascorbate in a Nucleic Acid-Preserving Composition

A stock solution of sodium ascorbate (250 mM) was prepared in a solution containing 30 mM Tris-HCl, pH 8.0, 30% ethanol, 3 mM CDTA. 20 μ L was removed at the indicated times, mixed with 50 mL of CB (see Example 8) and the absorbance at 265 nm was read immediately. The stock solution was maintained at room temperature. The results are shown in FIG. 8.

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

What is claimed is:

1. A device for receiving and preserving nucleic acid in a biological sample, said device comprising:

- a. one or more walls defining a containment vessel having a top having an opening, and a closed bottom having a sample receiving area for holding said biological sample, said opening for receiving a liquid sample and for sealably receiving a sealing cap, said top having an opening for receiving a biological sample from the mouth of a user and further comprising at least one marking on said one or more walls which corresponds to a fluid volume in the sample receiving area;
 - b. a reagent compartment having a barrier, said barrier sealing and containing reagents in said reagent compartment and capable of disestablishment to release said reagents into the sample receiving area;
 - c. reagents in the reagent compartment for preserving nucleic acids potentially present in the sample wherein said reagents comprise a denaturing agent, a chelator and a buffer agent; and,
 - d. the sealing cap, whereby the device is configured such that, when sealably closing said opening with said sealing cap, the barrier mechanically disestablishes to release said reagents to form a mixture of reagents and said biological sample wherein said buffering agent maintains a pH of said mixture equal to or above 5.0 to preserve nucleic acids potentially present in the sample.
2. The device of claim 1, wherein the biological sample comprises a bodily fluid.
3. The device of claim 1, wherein the biological sample comprises sputum.
4. The device of claim 1, wherein the biological sample comprises saliva.
5. The device of claim 1, wherein the denaturing agent comprises dodecyl sulfate.

6. The device of claim 1, wherein the chelator comprises ethylenediamine tetraacetic acid (EDTA).

7. The device of claim 1, wherein the reagents further comprise an antimicrobial agent.

8. The device of claim 1, wherein the reagents further comprise an antioxidant free-radical scavenger.

9. The device of claim 1, wherein the barrier comprises a septum.

10. The device of claim 9, wherein the septum is configured to be punctured or pierced to release the reagents to form a mixture of the released reagents and the biological sample.

11. The device of claim 10, wherein the biological sample comprises saliva.

12. The device of claim 11, wherein the denaturing agent comprises dodecyl sulfate.

13. The device of claim 12, wherein the chelator comprises ethylenediamine tetraacetic acid (EDTA).

14. The device of claim 13, wherein the buffering agent comprises TRIS.

15. The device of claim 14, wherein the buffering agent maintains pH of the mixture from about 7.0 and about 10.0.

16. The device of claim 15, wherein the reagents further comprise an antimicrobial agent.

17. The device of claim 16, wherein the reagents further comprise an antioxidant free-radical scavenger.

18. The device of claim 1, wherein the device is configured such that, upon sealably closing said opening with said sealing cap, the barrier is capable of permanent disestablishment.

19. The device of claim 1, wherein the device is configured such that, upon sealably closing said opening with said sealing cap, the barrier is permanently disestablished.

20. The device of claim 1, wherein the device is configured such that, upon sealably closing said opening with said sealing cap, the barrier displaces.

21. The device of claim 20, wherein the barrier is configured to disestablish when displaced by a linear actuator.

22. The device of claim 21, wherein the linear actuator comprises a plunger.

23. The device of claim 1, wherein sealably receiving the sealing cap comprises engaging a thread on the sealing cap and the opening.

24. The device of claim 23, wherein engaging the thread on the sealing cap and the opening comprises exerting a force on the barrier, wherein the force is perpendicular to a direction of rotation of the sealing cap.

25. The device of claim 24, wherein exerting the force on the barrier comprises displacing the barrier.

26. The device of claim 24, wherein a linear actuator exerts the force on the barrier.

27. The device of claim 1, wherein the barrier remains in a disestablished position while the opening is sealably closed by the sealing cap.

28. The device of claim 27, wherein the barrier is capable of returning to a pre-disestablished position when the sealing cap is not sealably closing the opening.

29. The device of claim 27, wherein the barrier is configured to be displaced from a pre-disestablished position to a disestablished position when sealably closing the opening with the sealing cap.

30. The device of claim 1, wherein the barrier remains intact when disestablished.

31. The device of claim 1, wherein sealably receiving the sealing cap comprises engaging the containment vessel and the barrier.

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32. The device of claim 31, wherein engaging the containment vessel and the barrier comprises engaging the sealing cap and a plunger, thereby engaging the plunger and the barrier.

33. The device of claim 1, wherein the barrier is configured to disestablish at room temperature.

34. The device of claim 1, wherein the sealing cap associates with the containment vessel to create a fluid-tight seal.

35. The device of claim 1, wherein at least partially dissociating the sealing cap from the containment vessel causes the barrier to close.

36. The device of claim 10, wherein the device further comprises a piercing member and wherein the piercing member is configured to puncture or pierce the septum to release the reagents to form a mixture of the released reagents and the biological sample.

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(12) **United States Patent**
Biadillah et al.

(10) **Patent No.: US 11,002,646 B2**

(45) **Date of Patent: May 11, 2021**

(54) **DEVICES, SOLUTIONS AND METHODS FOR
SAMPLE COLLECTION**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/879,506**

(22) Filed: **May 20, 2020**

(65) **Prior Publication Data**
US 2020/0284704 A1 Sep. 10, 2020

Related U.S. Application Data

(63) Continuation of application No. 16/023,772, filed on
Jun. 29, 2018, which is a continuation of application
(Continued)

(51) **Int. Cl.**
G01N 1/30 (2006.01)
A61B 10/00 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC **G01N 1/30** (2013.01); **A61B 10/007**
(2013.01); **A61B 10/0051** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC G01N 1/30; G01N 1/10; G01N 2001/305;
G01N 2001/002; G01N 1/28; B01L
3/502;
(Continued)

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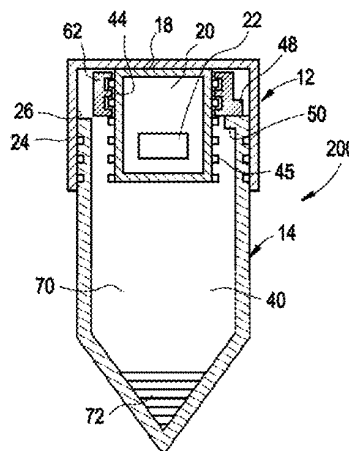
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(57) ABSTRACT

The disclosure relates to devices, solutions and methods for
collecting and processing samples of bodily fluids contain-
ing cells (as well as embodiments for the collection, and
processing and/or analysis of other fluids including toxic
and/or hazardous substances/fluids). In addition, the disclo-
sure relates generally to function genomic studies and to the
isolation and preservation of cells from saliva and other
bodily fluids (e.g., urine), for cellular analysis. With respect
to devices for collection of bodily fluids, some embodiments
include two mating bodies, a cap and a tube (for example),
where, in some embodiments, the cap includes a closed
interior space for holding a sample preservative solution and
mates with the tube to constitute the (closed) sample col-
lection device. Upon mating, the preservation solution flows
into the closed interior space to preserve cells in the bodily
fluid. The tube is configured to receive a donor sample of
bodily fluid (e.g., saliva, urine), which can then be subjected
to processing to extract a plurality of cells. The plurality of

(Continued)



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cells can be further processed to isolate one and/or another cell type therefrom. The plurality of cells, as well as the isolated cell type(s), can be analyzed for functional genomic and epigenetic studies, as well as biomarker discovery.

15 Claims, 9 Drawing Sheets

Related U.S. Application Data

No. 15/227,693, filed on Aug. 3, 2016, now abandoned, which is a continuation of application No. 14/127,832, filed as application No. PCT/US2012/043176 on Jun. 19, 2012, now Pat. No. 9,442,046.

- (60) Provisional application No. 61/498,584, filed on Jun. 19, 2011, provisional application No. 61/598,601, filed on Feb. 14, 2012, provisional application No. 61/598,618, filed on Feb. 14, 2012.

(51) Int. Cl.

B01L 3/00 (2006.01)

G01N 1/10 (2006.01)

G01N 1/00 (2006.01)

(52) U.S. Cl.

CPC **A61B 10/0096** (2013.01); **B01L 3/502** (2013.01); **G01N 1/10** (2013.01); **B01L 3/5021** (2013.01); **B01L 3/50825** (2013.01); **B01L 2200/025** (2013.01); **B01L 2200/0689** (2013.01); **B01L 2200/085** (2013.01); **B01L 2300/042** (2013.01); **B01L 2300/047** (2013.01); **B01L 2300/049** (2013.01); **B01L 2300/0832** (2013.01); **B01L 2400/0683** (2013.01); **G01N 2001/002** (2013.01); **G01N 2001/305** (2013.01)

(58) Field of Classification Search

CPC **B01L 2200/025**; **B01L 2200/0689**; **B01L 2200/085**; **B01L 2300/042**; **B01L 2300/0832**; **B01L 3/5021**; **B01L 3/50825**; **B01L 2300/047**; **B01L 2300/049**; **B01L 2400/0683**; **A61B 10/0051**; **A61B 10/007**; **A61B 10/0096**; **A01N 1/0273**; **A01N 1/0226**; **C12N 2509/10**; **C12N 5/0636**
See application file for complete search history.

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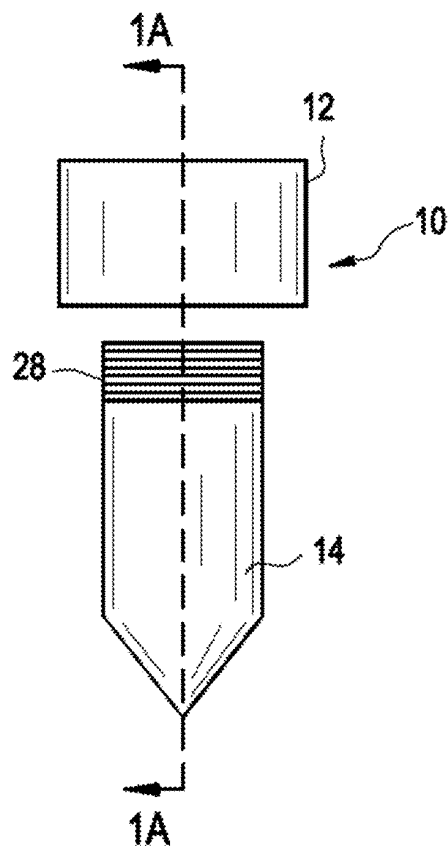
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FIG. 1



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FIG. 1A

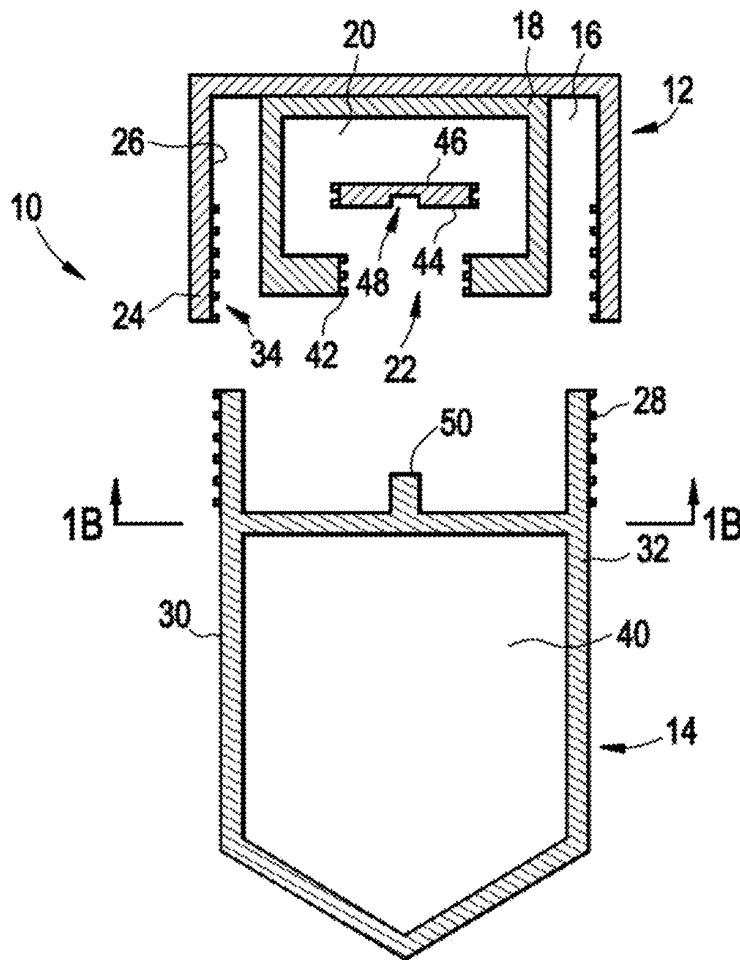
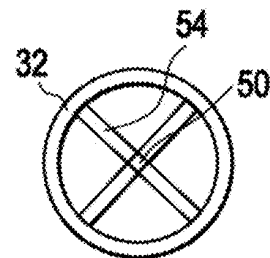


FIG. 1B



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FIG. 2A

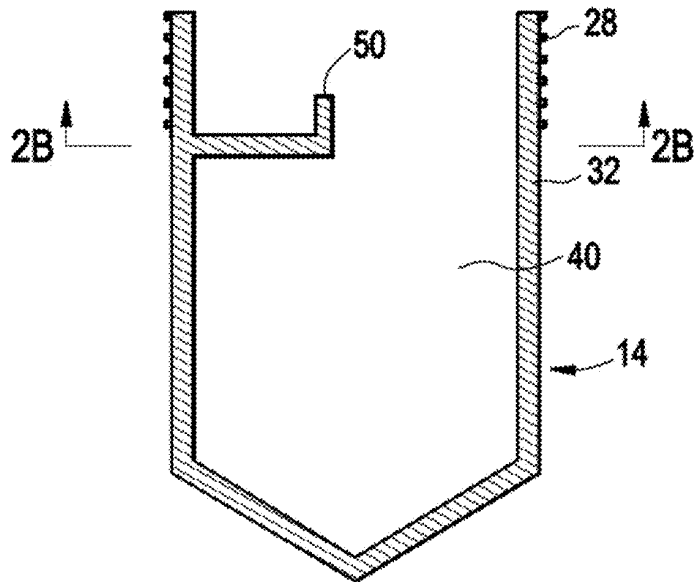
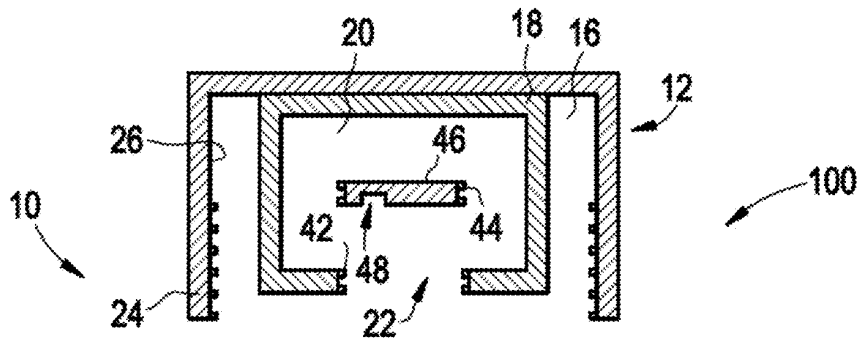
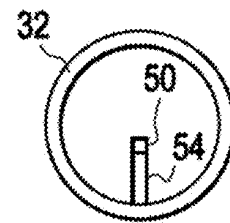


FIG. 2B



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FIG. 3A

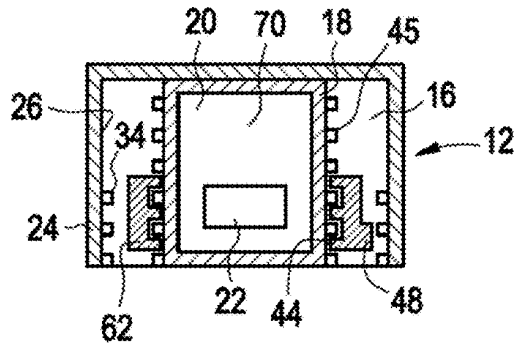


FIG. 3B

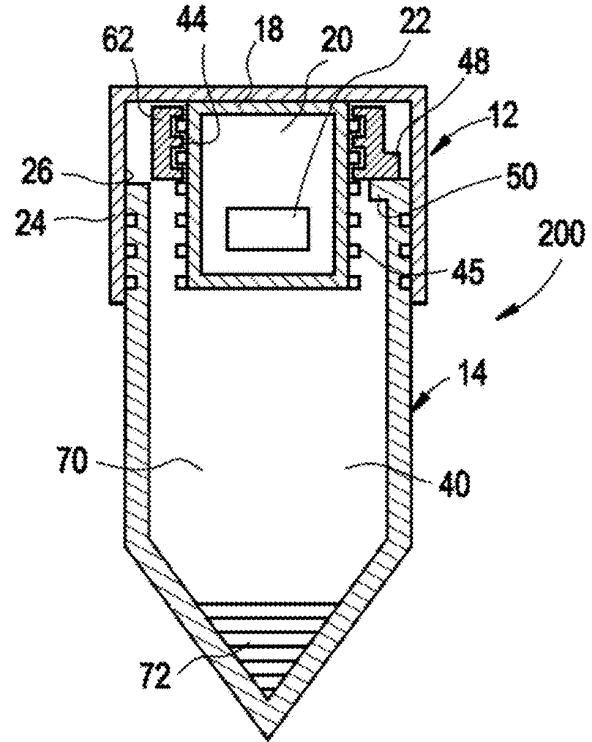
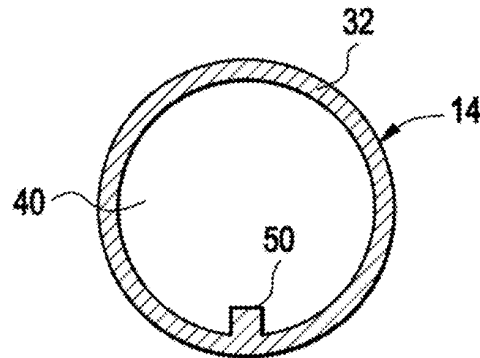


FIG. 3C



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FIG. 4A

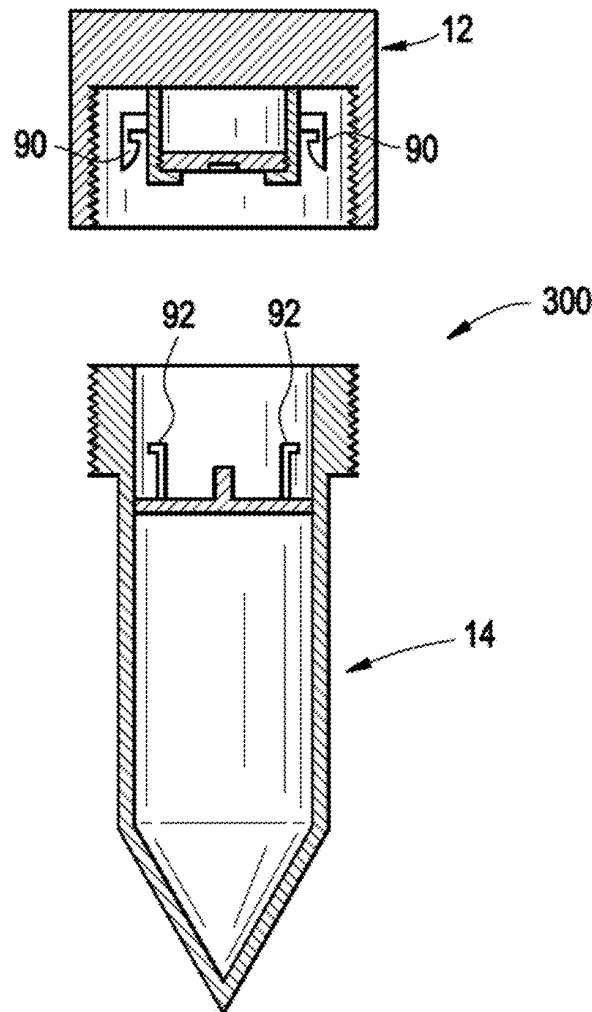
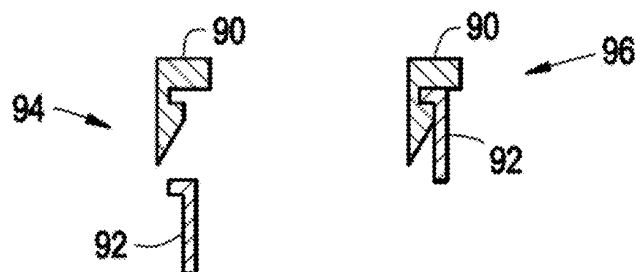


FIG. 4B



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FIG. 5A

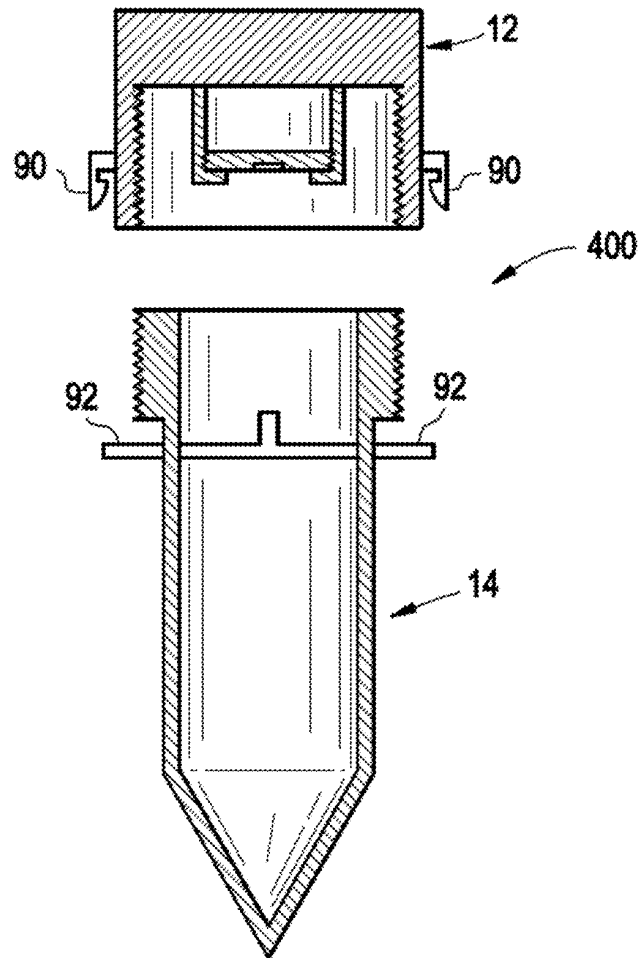


FIG. 5B

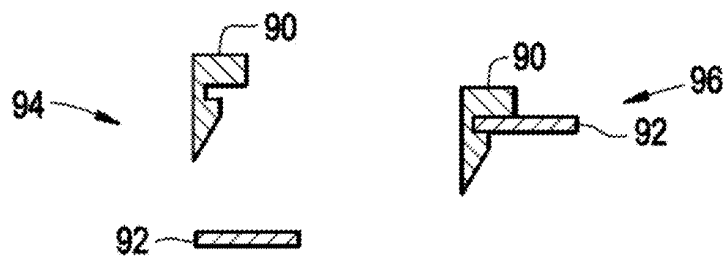


FIG. 6

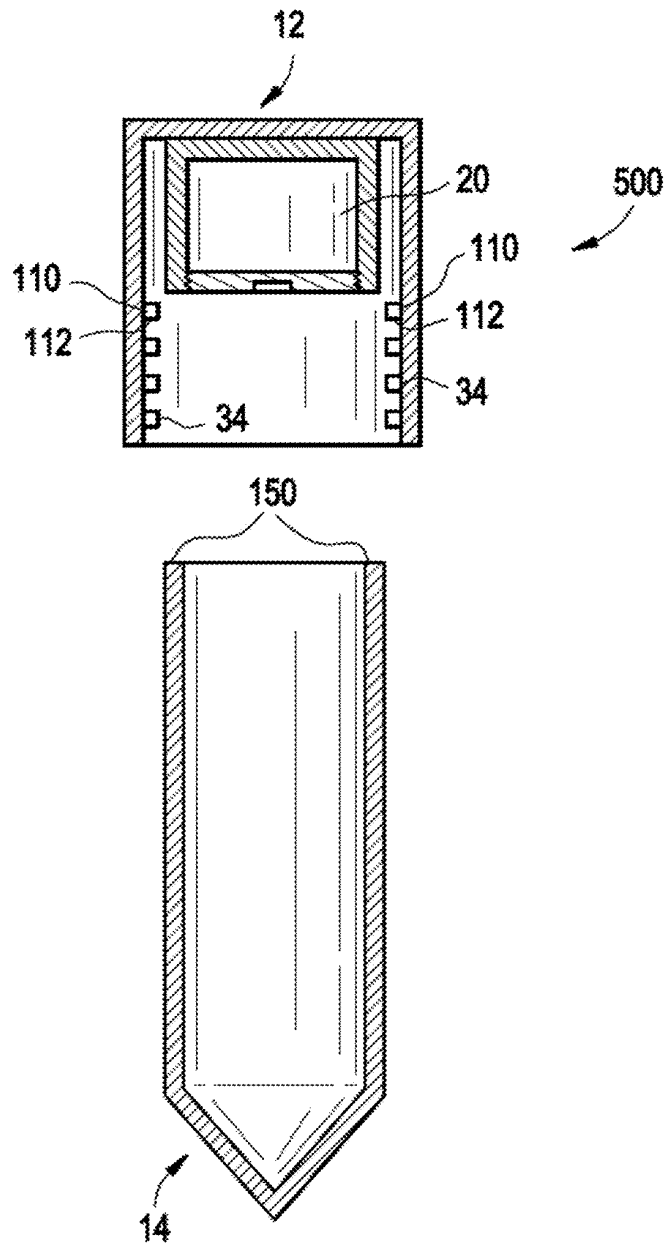


FIG. 7A

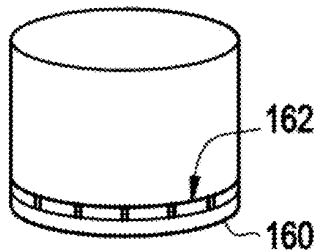


FIG. 7B

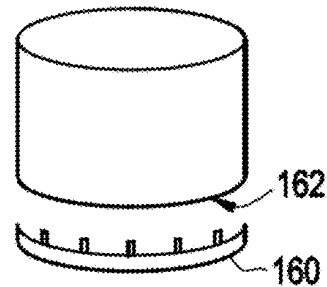


FIG. 8

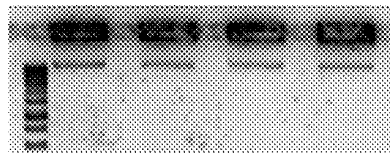
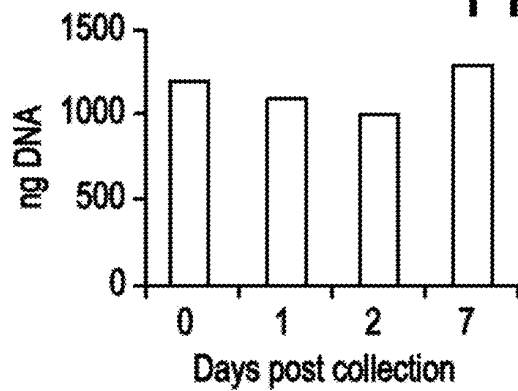


FIG. 9

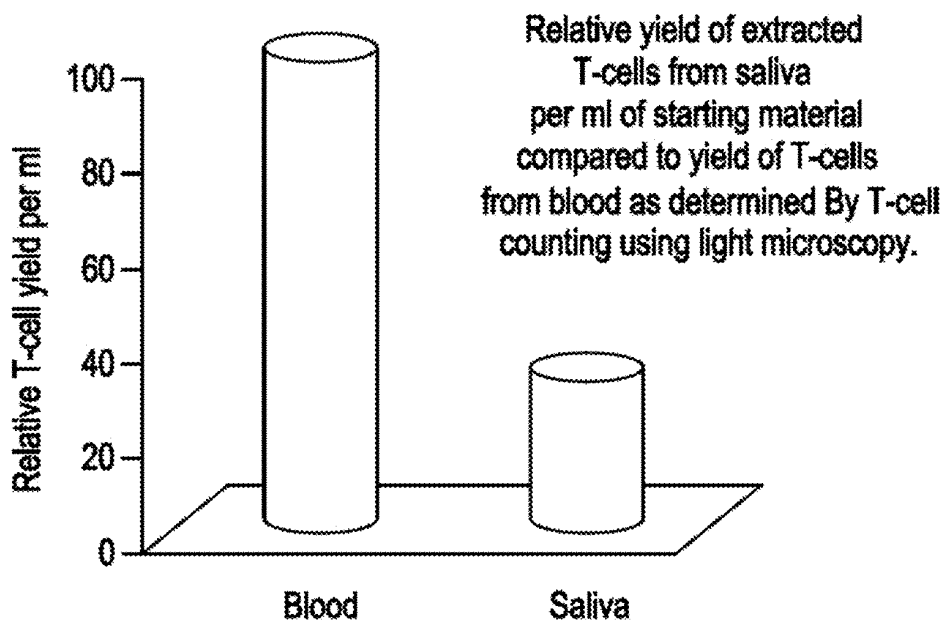
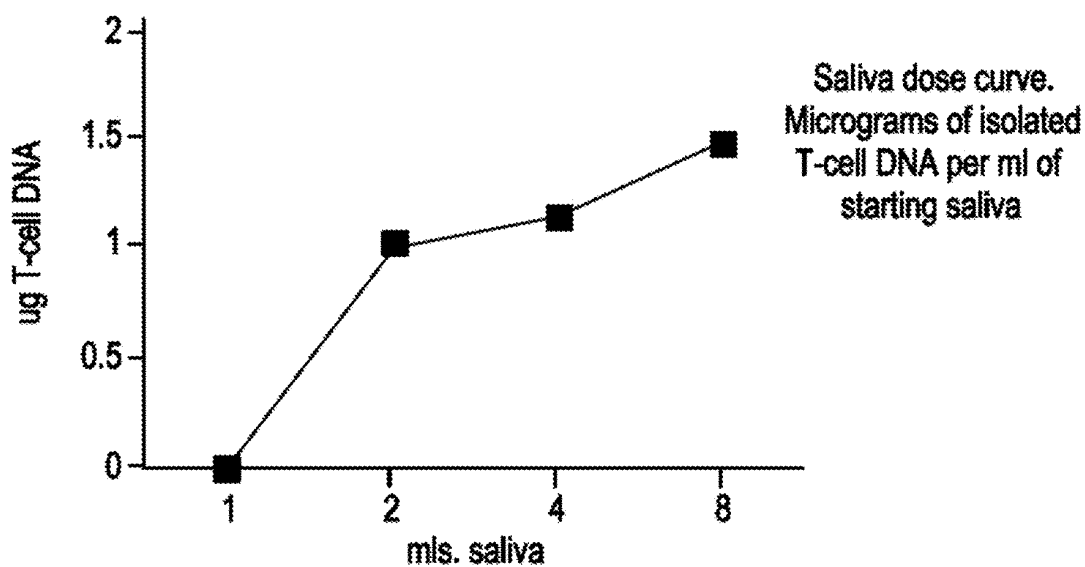


FIG. 10



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**DEVICES, SOLUTIONS AND METHODS FOR
SAMPLE COLLECTION**

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 16/023,772, filed Jun. 29, 2018, which is a continuation of U.S. patent application Ser. No. 15/227,693, filed Aug. 3, 2016, which is a continuation of U.S. patent application Ser. No. 14/127,832, filed Dec. 19, 2013, now U.S. Pat. No. 9,442,046, which is a 35 U.S.C. § 371 national stage entry of PCT/US2012/043176, filed Jun. 19, 2012, and claims priority under 35 USC § 119(e) to U.S. provisional patent application Nos. 61/498,584, filed Jun. 19, 2011, 61/598,601, filed Feb. 14, 2012, and 61/598,618, filed Feb. 14, 2012. Each disclosure of the foregoing is herein incorporated by reference in its entirety.

Field of the Disclosure

The disclosure relates to devices, solutions and methods for collecting samples of bodily fluids or other substances, including hazardous and/or toxic substances, and in particular, a naturally expressed bodily fluid (e.g., saliva, urine). In addition, the disclosure relates generally to functional genomics and to the isolation and preservation of cells from such bodily fluids, for studies in any of: functional genomic and epigenetic studies, and biomarker discovery (for example).

Background

Personalized medicine is the customization of treatment to an individual as opposed to the one treatment-for-all model. Personalized medicine involves categorizing a patient based on his or her physical condition and designing an optimal healthcare solution exclusively for that category. The progression of personalized medicine is dependent on the discovery, validation, and commercialization of biomarkers to stratify populations for treatment and for the development of diagnostics for screening and early detection.

Epigenetic research has come to the forefront of medical research and is implicated in the etiology of a number of physical and mental illnesses including: cancer, obesity, diabetes, schizophrenia, and Alzheimer's disease (Alika et al., 2010; Grant et al. 2010; McGowen et al., 2009; McGowen and Szyf, 2010; Plazas-Mayorca and Vrana, 2011; and Portela and Esteller, 2010). In addition, Epigenetics may hold particular promise in the many scientific and medical areas including but not limited to: cancer, diabetes, drug integrations, drug effectiveness, childhood aggression, suicidal behaviors, aging, inflammation, pain, obesity, schizophrenia, and other mental illnesses (Abdolmaleky et al., 2005; Costa et al., 2003; Iwamoto & Kato, 2009; Kuratomi et al., 2007; McGowan & Kato, 2007; McGowen and Szyf, 2010; Peedicayil, 2007; Petronis et al., 1999; McGowen and Szyf, 2010; Plazas-Mayorca and Vrana, 2011; and Zawia et al., 2009).

A major challenge in the field includes the identification of an appropriate source material for home-based sample collection that is adequate for large-scale epigenetic research including whole-genome-analysis studies. Epigenetics may be the key for understanding the mechanisms of gene-environment interactions as growing evidence suggests that epigenetic mechanisms may provide a molecular memory of environmental experiences (Ho, 2010; Kappeler and

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Meaney, 2010; McGowen et al., 2009, McGowen and Szyf, 2010; Portela and Esteller, 2010; Richards, 2008; Russo et al., 2010; Tsai et al, 2010; and Vlaanderen et al., 2010). Preliminary data from some humans suggest that distinct methylation patterns in peripheral blood cells are associated with social behaviors including: childhood aggression, suicidal behaviors, and ageing (Kappeler and Meaney, 2010; McGowen et al., 2009; McGowen and Szyf, 2010; Portela and Esteller, 2010; Russo et al., 2010, Tierling et al., 2010; Tsai et al, 2010; and Zhang et al., 2011).

Due at least in part to the heterogeneous nature of human disease, particularly mental illness, and the complex interaction of contributing etiological factors, studies require large sample sizes to provide reliable and significant effects. However, current research options for sample collection for epigenetic studies do not meet this requirement of "large sample sizes." The need for large sample sizes for studies is also true in order to produce significant effects in regards to studying human-environment interactions as these interactions are also of a very complex nature with many contributing factors. The ability to perform large-scale "population sized" (subject samples numbering in at least the hundreds to thousands) epigenetic research can introduce a new understanding of human-environment interaction and facilitate the completion of longitudinal studies facilitating the development of epigenetic-based screening diagnostics crucial to the progression of modern medicine. This epigenetic research may lead to a new understanding of how the environment affects our epigenome and how this relates to a person's health outcome, which may further lead to the development of preventative interventions for individuals who are considered high-risk and diagnostics for these health disparities including, but not limited to, diagnosis.

Some epigenetic studies attempting to quantify environmental and other complex interactions in human populations use blood as the source material for experimentation. Blood can restrict the researcher's ability to conduct large population-sized studies as it:

1. generally requires medical supervision,
2. involves invasive procedures for collection,
3. carries stigma that limits participation, and
4. is expensive to collect and ship.

Naturally expressed bodily fluids, e.g., saliva and urine, can be an additional or alternative appropriate source material for home-based sample collection as they:

1. do not require invasive techniques,
2. do not have the same stigma as blood,
3. do not require professional supervision, and
4. can be inexpensive to collect.

In addition, at least saliva has been shown to contain white blood cells (Dos-Santos et al., 2009). The use of bodily fluids, e.g., saliva, urine, may enable large-scale "population-sized" epigenetic research. In addition, home-base sample collection of saliva, or urine, may allow for a much wider range of research options available as it can greatly increase participant numbers and samples can be more easily shipped by the subjects from anywhere in the world. For example, the ability to more easily ship samples from anywhere in the world can be particularly useful when samples are from countries that do not have laboratory infrastructure.

An organism's genome is a fixed sequence that contains its hereditary information and is the same in every cell of an organism. An organism's epigenome, by contrast, varies between cell types and changes over the organism's lifetime. Thus, epigenetic studies may include a single cell type as the source of sample material to control for these differences

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(Johnson and Tricker, 2010; Lister et al., 2009; and Rangwala et al., 2006). For example, human saliva contains numerous cell types, including epithelial cells, cells normally found in the blood (i.e., T-cells and B-cells), bacteria and debris (Dos-Santos et al., 2009 and Viet and Schmidt, 2008). The cells in saliva that are the most important to profile epigenetically are those that come from the blood stream, as these cells carry epigenetic information from the entire body (Kappeler and Meaney, 2010; McGowen and Szyf, 2010; McGowen and Szyf, 2010; Righini et al., 2007; Rosas et al., 2011, Vlaanderen et al., 2010 and Zhang et al., 2011).

Additionally, it may not be practical to use whole saliva DNA as the cells in saliva that are not found in the blood, such as epithelial cells, which make up the vast majority of cells in saliva (Dos-Santos et al., 2009) have the ability to “mask” the epigenetic effects seen in T-cells (cells that originated in the blood) by dampening the effect of the minority of cells (Dos Santos et al., 2009, Lister et al., 2009; and Tierling et al., 2010). To address these concerns AboGen developed a method to separate and extract the different cell types found in bodily fluids such as saliva by taking advantage of cell-specific markers and isolation techniques (e.g., magnetic). This method uses practical amounts of bodily fluids, such as saliva, to yield enriched cells that can be used for downstream biological applications including large-scale functional genomic studies (example epigenomic studies). For example, saliva sample processing technology allows collected samples to be processed into single cell types and have their epigenomes profiled.

Furthermore, saliva (and other bodily fluids) can present challenges with cell isolation as a source material for blood cells in respect to downstream experimentation for reasons such as:

1. Blood is a transporter fluid while saliva is a digestive fluid that can be rich in proteases, enzymes and secreted substances and urine is a excretory fluid consisting of unwanted waste products.
2. Some fluids can have a wide pH range and some of the pH values reported, such as for saliva, would result in death if blood reached that pH (saliva is 6.2-7.4; urine is 4.5-8; blood is 7.35-7.45).
3. Some fluids contain more bacteria than blood.
4. Some fluids contain non-cellular material that varies between individuals and interferes with cell isolation.
5. Some fluids include blood cells, such as T-cells, which can be abundant in blood, but may be rare in other naturally expressed bodily fluids, such as saliva or urine, and are vastly outnumbered by other cell types, such as epithelial cells, unlike in blood.
6. The subset of lymphocyte cells in some bodily fluids, such as saliva, greatly differs from the population of those cell types in blood. For example, only CD4+ CD8- T-cells are reported to be found in saliva.
7. Some fluids are produced each day, such as saliva at about a rate of 0.5-1.5 liters per day per person.

Therefore, there is a need for new methods for isolating rare cells (i.e., T-cells) from saliva and other naturally expressed bodily fluids.

For collecting saliva samples from a large population of people (example: functional genomic studies) who are widely geographically dispersed, several requirements may need to be met for an optimal sample collection device. For example, it may be beneficial to have the sample collection device securely house a toxic preservative solution in a closed chamber. Additionally, the sample collection device may be able to be sent to a donor with the toxic solution

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safely enclosed. The sample collection device may also allow easy and safe collection of a donor specimen, such as human saliva or urine, with no risk of exposure of the donor to the toxic solution. Furthermore, the sample collection device may allow the donor to safely mix the toxic solution and the specimen (for preservation of the specimen) with no risk of exposure of the donor to neither the toxic solution nor any other hazard. The sample collection device may also allow the donor to send the sample collection device to a laboratory for processing generally “as-is” after securely closing the sample collection device. Finally, the sample collection device may further allow a laboratory technician to receive the sample collection device and safely open it for processing with generally no risk of exposure to any hazards.

Some currently available sample collection devices include, for example, U.S. Pat. No. 7,482,116 which describes a device that utilizes disassociating a barrier to allow fluid communication between a cavity holding the donor sample and a solution, however, embodiments included in the patent are limited to the use of sharp extruding objects and thin pierceable membranes. The thin pierceable membranes can represent a safety hazard to the sample donor as any wrong manipulation (such as with a finger nail) can lead to piercing of the membrane and release of the solution. US patent publication no. 2009/0216213 A1 claims a device that utilizes a pierceable membrane to establish fluid communication between a cavity containing a solution and the donor sample. This can represent a safety hazard to the sample donor as any wrong manipulation can lead to piercing the membrane and exposing the solution. The device also requires exchange of the cap prior to sending the sample to the end user. This can represent a safety hazard as it may expose the sample donor to the potentially toxic solution. Therefore, there is a need for safer and easier to use sample collection devices.

Additionally, the purification process requires cells to maintain their antigen profiles and the epigenomic profiling requires that their epigenome be maintained. To this end, it is necessary to treat the cells in such a way that they are able to generally maintain these features. Currently available treatments generally do not meet this need. For example, U.S. Pat. Nos. 7,267,980 and 7,749,757 disclose solutions containing lysine, glycine and formaldehyde for stabilizing cells from blood. However, those solutions will not protect cells from proteases found in some bodily fluids, such as saliva. Therefore, there is a need for new solutions and methods that will preserve the antigenicity and epigenome of cells in other bodily fluids, such as saliva.

SUMMARY OF THE DISCLOSURE

Embodiments of the disclosure provide safer and easy to use sample collection devices for naturally expressed bodily fluids (for example), as well as solutions and methods for preserving cells of samples collected, and additionally, methods for isolating specific cells either collected and/or preserved. Such isolated cells (and even non-isolated collected cells), can then be analyzed for studies in any of: functional genomic and epigenetic studies, and biomarker discovery (for example).

The sample collection devices according to the present disclosure provide several advantages over currently available sample collection devices. For example, in some embodiments, the sample collection devices use a minimum amount of parts and do not require removal or exchange of a piece or an object thereof. In some embodiments, the

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sample collection devices do not require any additional manipulation by the sample donor apart from depositing the sample in the sample collection device and closing the sample collection device. In some embodiments, use of the sample collection devices provide improved safety for both the sample donor and the end user, since, for example, sharp objects are not included and there is limited to no risk of exposure to toxic solutions (e.g., sample preservative solutions).

In some embodiments of the sample collection device, the sample collection device can have two main mating bodies, a cap and a tube. The cap can include a closed cavity holding a preservative solution which can mate with the tube to constitute the closed sample collection device. The tube can be configured to receive the donor specimen. The cap and tube are configured so that when the donor deposits the specimen and closes the tube with the cap, the cavity holding the preservative solution may be opened to release the preservative solution and allow it to mix with the donor specimen.

In some embodiments, a bodily fluid sample collection device for the collection of naturally expressed bodily fluids is provided and includes a cap having an outer wall having an engagement member, and an interior chamber for holding a fluid. The chamber may comprise inner walls which define an interior space and an aperture, where the aperture is configured for sealing by a removable blocking member. The blocking member may include a first coupling member for engaging a corresponding second coupling member in a tube, thereby causing removal of the blocking member and opening of the aperture when the cap is coupled to the tube. The device also includes the tube which includes a containment wall defining a reservoir for bodily fluid sample collection, an engagement member complementary to the engagement member of the cap, and the second coupling member.

In some embodiments, one and/or another of the following features may be provided with a sample collection device:

- the removable blocking member is a disk-shaped member which threadably engages the aperture;
- the first coupling member comprises an indentation disposed centrally in the bottom of the blocking member and the second coupling member is disposed centrally within the tube;
- the first coupling member comprises a recess disposed eccentrically in the bottom of the blocking member and the second coupling member is disposed eccentrically within the tube;
- the removable blocking member comprises an annular member having threads arranged thereon, where the annular blocking member substantially covers the aperture, and the inner wall of the cap includes complementary threads, such that the annular member can be screwed into the interior space to uncover the aperture;
- a locking mechanism, to lock the cap to the tube (or lock any two components together), the locking mechanism may comprise a wedge and a complementary flange;
- a sealing mechanism which may comprise a sealing substance associated with the engagement member of the cap, where upon coupling the cap to the tube, the sealing substance flows into at least the engagement member of the cap;
- tamper-evident means for determining whether the cap has been opened, which may comprise a ring having a first portion thereof integral with an open end of the cap, where upon the cap being coupled to the tube, the

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ring is positioned adjacent the tube; as such, in some embodiments, upon the cap being de-coupled from the tube, the first portion is broken and the ring remains substantially adjacent the tube; and/or the fluid in the cap chamber comprises a solution for preserving cells.

In some embodiments, a bodily fluid sample collection device for the collection of naturally expressed bodily fluid is provided and includes a cap having an interior chamber for holding a fluid and a first engagement member, and a tube comprising a containment wall defining a reservoir for sample collection and a second engagement member for engagement to the first engagement member. In some such embodiments, the cap comprises an outer wall having the first engagement member, the chamber comprises inner walls defining an interior space which holds the fluid, and an aperture, the aperture being configured for sealing by a removable blocking member. In addition, in some embodiments, the blocking member includes a first coupling member for engaging a corresponding second coupling member of the tube, where upon the coupling of the cap to the tube, the blocking member is moved and the aperture opens.

In some embodiments, a method for collecting a sample of a naturally expressed bodily fluid (or toxic or hazardous fluid) is provided and includes providing a bodily fluid collection device according to any of the disclosed sample collection device embodiments, depositing the bodily fluid into the chamber, and mating the cap and tube together such that the corresponding engagement members engage, where the blocking member moves and the preservation fluid flows into the reservoir containing the bodily fluid such that cells contained in the bodily fluid are preserved for analysis. In some such embodiments, further steps may include at least one of (with reference to bodily fluids): isolating one or more cell types for a plurality of cell types in the bodily fluid, and analyzing the collected cells.

As one of skill in the art will appreciate, in some embodiments, at least one of DNA, RNA and proteins can be extracted from collected/preserved cells, whether the isolated cells, or non-isolated cells.

In some embodiments, a kit for the collection of naturally expressed bodily fluids (or toxic and/or hazardous fluids) is provided and comprises a plurality of sample collection devices according to of the disclosed sample collection devices.

In addition, the current disclosure relates to functional genomic studies including epigenetic studies. More particularly, this disclosure also relates to the isolation of cells from bodily fluids, such as saliva and urine, for these studies. Accordingly, some embodiments of the disclosure include methods for preserving the antigenicity and epigenome of cells, and isolating rare cells, including, without limitation T-cells from bodily fluids, such as saliva and urine, are disclosed herein.

As used herein, the collection of "bodily fluids" generally refers to the collection of naturally expressed bodily fluids (although some embodiments can be used for collection of intravenous collection methods—e.g., blood). Thus, with references to the disclosed embodiments, "bodily fluids" refer to naturally expressed bodily fluids including, for example, saliva and urine.

For example, in some embodiments, a solution for preserving cells in bodily fluids, such as saliva and urine, is provided for further separation into cell types and downstream analysis that allows for the cells in saliva to retain their antigenicity and cellular architecture during storage. The solution can contain at least one chemical fixing agent, such as but not limited to paraformaldehyde, and at least one

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protease inhibitor. In some embodiments, the solution may further contain, for example, one or more of: at least one antimicrobial agent, serum proteins from human and/or other animal species. The solution may be buffered at a pH between about 6.4 to about 8.4, and in some embodiments, between about 7.2 to about 7.6.

In some embodiments, a method for preserving cells in one or more bodily fluids includes contacting collected cells with a solution according to one and/or another embodiment of the present disclosure, which allows the cells to retain their antigenicity and epigenome, for example.

In some embodiments, a method for isolating cells from chemically fixed cells collected from a bodily fluid, e.g., saliva or urine, and includes centrifuging the cells to separate, for example, DNA and/or other soluble material from a pellet of cells, bacteria, and debris, enriching white blood cells from other contents of the pellet, and isolating specific cells (e.g., white blood cells) using antibodies conjugated to magnetic beads targeted to cell specific markers.

In some embodiments, methods for isolating a particular type of cell, for example, a type of white blood cell (e.g., lymphocytes), from one or more bodily fluids (e.g., saliva and/or urine), and includes one or more of the following steps (and, depending upon the embodiment, several or all of the following steps): providing a sample of bodily fluid comprising chemically fixed cells, optionally centrifuging the bodily fluid sample to obtain a pellet comprising cells, optionally re-suspending the pellet in a buffer, subjecting the re-suspended pellet to density gradient separation to obtain a layer of a mixture of white blood cell types (including lymphocytes), contacting the mixture of cell types with a solution containing specific binding agents for an epitope found on a particular type of white blood cell, and separating the particular type of white blood cell (including lymphocytes) from the mixture of white blood cell types.

In some embodiments, the specific binding agents may be magnetic beads coupled to antibodies specific to an epitope found on a particular type of white blood cell, and in the separation step may then comprise, for example, magnetically separating the particular type of white blood cell (including lymphocytes) from the mixture of white blood cell types (though other cell separation techniques are within the scope of the disclosure).

In some embodiments, the bodily fluid (e.g., saliva, urine) can be mixed with a chemical fixative solution and the mixture can be removed from the pellet. The pellet can then be re-suspended in a buffer. The re-suspended pellet may optionally be centrifuged and washed one or more times in the buffer. The washed pellet may then be applied to a hydrophilic polysaccharide mixture to form a gradient. This gradient may be different than that used for blood because the density of the cells in other bodily fluids (e.g., saliva, urine) after chemical fixation for preservation can be different due to the different density of the preserved cells requiring an alteration in the time, temperature, and/or density of the gradient for the cells to be processed through this density gradient.

Additionally, in some embodiments, the white blood cells can form a layer in the gradient. The white blood cell layer can be extracted from the gradient and placed in another centrifuge tube where it may be washed in a buffer and re-pelleted to remove the remaining gradient mixture. The pellet may then be re-suspended and incubated in a buffer containing antibodies that are conjugated to magnetic beads and specific to antigens that are specific for a cell type to be isolated. In some embodiments, the cell type to be isolated is T-cells and the antigen is a T-cell-specific antigen. In some

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embodiments, the antigen is CD4. The re-suspended cells in the buffer can be bound by the antibody and subjected to a magnetic field that magnetically attracts the cells bound to the antibody-conjugated magnetic beads to the side of the tube. Remaining liquid may then be removed from the tube and the tube is washed in buffer. Isolated T-cells then remain attracted to the side of the tube and are ready for further processing, such as freezing for later downstream experimentation (for example).

In some embodiments, a method for preserving cells in a naturally expressed bodily fluid comprises contacting the bodily fluid with the preservation solution according to any of the disclosed embodiments.

The devices, solutions and methods of sample collection, preservation, isolation and analysis will be better understood in light of the following drawings, detailed description and claims. Like reference symbols in the various drawings indicate like elements.

It is worth noting that while some embodiments of the sample collection devices disclosed herein are set forth for use with the collection of bodily fluids, the same also has particular use with the collection of any other substance, including hazardous and/or toxic fluids.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a sample collection device comprising a cap and a tube according to some embodiments of the present disclosure.

FIG. 1A is a cross section view taken along line 1A-1A of FIG. 1 and shows the interior chamber of the cap comprising inner walls which define an interior space and an aperture according to some embodiments of the present disclosure.

FIG. 1B is a cross section view taken along line 1B-1B of FIG. 1A and shows a coupling member centrally positioned within the tube according to some embodiments of the present disclosure.

FIG. 2A shows a longitudinal cross section view of a sample collection device in which the cap contains an inner chamber with a removable blocking member that has an eccentrically located coupling feature which can mate with a coupling member eccentrically located in the tube according to some embodiments of the present disclosure.

FIG. 2B is a cross section view taken along line 2B-2B of FIG. 2A and shows a coupling member eccentrically positioned within the tube according to some embodiments of the present disclosure.

FIG. 3A shows an embodiment of the cap of the sample collection device in which the cap contains an inner chamber with a movable annular member that can cover an aperture in the inner wall according to some embodiments of the present disclosure.

FIG. 3B shows an embodiment of the sample collection device in which the cap is coupled to the tube and the movable annular member is moved to a position where it does not cover an aperture in the inner wall according to some embodiments of the present disclosure.

FIG. 3C is a top view of the tube shown in FIG. 2B and shows a coupling member positioned within the tube according to some embodiments of the present disclosure.

FIG. 4A shows an embodiment of the sample collection device comprising a locking mechanism disposed within the inside of the cap and the tube, which prevents the cap from being removed by at least the donor after the cap has been coupled to the tube according to some embodiments of the present disclosure.

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FIG. 4B shows the locking mechanism in the sample collection device shown in FIG. 4A showing a locked configuration and an unlocked configuration according to some embodiments of the present disclosure.

FIG. 5A shows a sample collection device comprising a locking mechanism disposed on an outer surface of the cap and tube, which prevents the cap from being removed by at least the donor after the cap has been coupled to the tube according to some embodiments of the present disclosure.

FIG. 5B shows the locking mechanism in the sample collection device shown in FIG. 5A showing a locked configuration and an unlocked configuration according to some embodiments of the present disclosure.

FIG. 6 shows a sample collection device further including a sealed cavity containing a sealing solution that is released into the engagement features of the cap and tube when the cap is coupled to the tube, which prevents the cap from being removed by at least the donor after the cap has been coupled to the tube according to some embodiments of the present disclosure.

FIG. 7A shows a “tamper-evident” cap, in which an annular member at the bottom of the cap can break away from the cap if the cap has been removed after having been rotated/screwed onto the tube according to some embodiments of the present disclosure.

FIG. 7B shows the “tamper-evident” cap shown in FIG. 7A showing the annular member broken away from the cap according to some embodiments of the present disclosure.

FIG. 8 shows the time course of DNA yield in samples stored in chemical fixative solution at room temperature after 0, 1, 2 and 7 days, as well as DNA extracted from T-cells from each sample according to some embodiments of the present disclosure.

FIG. 9 is a chart illustrating the relative yield of extracted T-cells per ml of starting material (e.g., sample of bodily fluid), as compared to a yield of T-cells from blood.

FIG. 10 shows a saliva dose curve of micrograms of isolated T-cell DNA per ml of saliva according to some embodiments of the present disclosure.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Embodiments of the present disclosure include devices, solutions and methods for the collection of samples, such as bodily fluids, as well as methods for isolating one or more cell types from collected cells (chemically fixed or otherwise). For example, in some embodiments, the sample collection devices provide several advantages over currently available sample collection devices, and in addition, the sample collection devices according to some embodiments use a minimum amount of parts and the devices do not require removal or exchange of a piece or an object. Furthermore, in some embodiments, the sample collection devices may generally not require additional manipulation by the sample donor apart from depositing the sample and closing the collection device. The sample collection devices according to some embodiments include improved safety of use for both sample donors and end users due, at least in part, to the elimination of sharp objects and limited risk of exposure to toxic solutions, as will be described in greater detail below.

In some embodiments, methods for the preservation and isolation of cells from bodily fluids for functional genomic and epigenetic studies, as well as biomarker discovery, are provided. Additionally, this disclosure provides devices, solutions and methods for isolating rare preserved cells,

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such as T-cells, from bodily fluids (i.e., saliva, urine), as will also be described in greater detail below.

Some embodiments of the sample collection device may include two mating bodies, such as a cap and a tube. In some embodiments, the cap may include a closed cavity, such as an interior space, for holding a preservative solution (which may be toxic) for mating with the tube to constitute a closed sample collection device. The tube may be configured to receive a donor specimen, such as one or more bodily fluids (e.g., saliva, urine). In some embodiments, the cap and/or tube may be configured so that when the donor deposits the specimen and closes the tube with the cap, the cavity in the cap, which may be holding the preservative solution, can be opened to release the preservative solution and allow it to mix with the donor specimen.

One of skill in the art will appreciate that with respect to some embodiments of the collection device described herein, such may be used in combination with accessories that ease specimen deposit within the collection device, including, for example, mouth adapters for saliva collection, funnels and hoses for urine collection, and the like.

In some embodiments, the sample collection device may comprise a cap having an outer wall with interior threads. Additionally, the sample collection device may include an interior chamber for holding a fluid with the chamber comprising walls defining an interior space and a threaded aperture in the wall. The aperture in the wall may be sealed by a threadably removable blocking member, where the blocking member may include engaging members for engaging a coupling member in a tube, thereby causing the blocking member to be removed and the aperture to open when the cap is threaded onto the tube (in some embodiments). In some embodiments, the sample collection device may further include a tube comprising a containment wall defining a lumen or reservoir for sample collection, exterior threads complementary to the interior threads of the outer wall of the cap, and a coupling member that has a shape which is complementary to the engaging member in the cap.

In some embodiments, the threadably removable blocking member can be a disk-shaped member that is at least one of pushed, rotated, screwed, threaded, and/or mated into the aperture of the inner chamber and can be at least one of pushed, rotated, screwed, threaded, and/or mated into the chamber by interaction between the engaging member of the cap and the coupling member of the tube when the cap is rotated or screwed onto the tube. The engaging member can be either centrally or eccentrically located in the disk-shaped member, with the coupling member being at least one of centrally or eccentrically located in the tube, respectively.

The terms push, rotate, screw, mate as well as thread, couple, and attach, as well as any corresponding tenses and plurals thereof (as additionally including the term “feature(s)”, disclosed herein, correspond to structure (well known to those of skill in the art) for connection (either permanent or temporary) of two (or more) components (e.g., “screw means” “mating means”, “coupling feature”, “engagement feature”). For example, with respect to “pushing”, such means can cover a “snap-fit” type of structure; rotation means can cover means in which a protruding member is received by a corresponding recess when one component is rotated relative to another. “Screwed” and “threadably” covers helical threaded engagement and the like. Thus, use of any of these terms (or tenses thereof) can also cover such connection with any such means or the equivalents thereof.

In some embodiments, a threadably movable annular member may not fit into the aperture, but rather covers the aperture from the outside of the inner chamber. In such

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embodiments, the annular member can have interior threads complementary to threads on the outside of the inner chamber or interior space. Interaction between the coupling features of the annular blocking member and the coupling member of the tube can cause the annular member to be screwed up the outside of the inner chamber, away from the aperture.

In some embodiments, the sample collection device may further include locking or sealing means, such that the cap cannot be removed from the tube by the donor once the cap has been connected or screwed onto the tube, such as by the donor. Suitable locking members can include a wedge on the cap and a matching flange on the tube or visa-versa. The wedge and flange can either be on the inside of the cap and tube, or on the outside of the cap and tube. Suitable sealing means include a sealed cavity containing a sealing solution, such as a glue, wherein the sealing solution is released when the cap is pushed, rotated or screwed onto the tube and thereafter cures in order to prevent disengagement between the cap and tube. In some embodiments, the sealing solution may be a two-component glue, such as an epoxy, with one component being sealed into the cap, and the other component sealed into the tube, such that the two components mix within the threads when the cap is screwed onto the tube. In other embodiments, the sealing solution can be a single component, such as a cyanoacrylate-based glue, which can be in a sealed cavity in the cap or tube, such that the sealing solution is released into the threads when the cap is screwed onto the tube. In some embodiments, the sealing solution can cure soon after engagement between the cap and tube such that disengagement between the tube and cap by the user can be generally prevented.

Alternatively, or in addition, some embodiments may further include an annular member at the base of the cap that is partially secured to the cap, such that removal of the cap after it has been screwed onto the tube breaks the bond between the cap and the annular member, thereby indicating that the tube has been opened. This "tamper-evident" embodiment is similar to those used to attach a cap to a soda bottle.

The sample collection devices according to some embodiments can be made of any suitable plastic, such as polypropylene, polystyrene and polycarbonate. The dimensions of the device can be modified to suit the specific processing the sample will be subjected to. In certain embodiments, typical dimensions include the following. For the inner chamber of the cap, the volume is from about 3 ml to about 10 ml, typically about 6 ml. For the lumen of the tube, the volume is from about 15 ml to about 50 ml, typically about 25 ml. Other volumes are within the scope of some embodiments of the present disclosure.

With respect to the figures, FIG. 1 is an illustration of an embodiment of a sample collection device 10 comprising a cap 12 and a tube 14. The tube can be configured for collection of one or more sample bodily fluids, and the cap can be configured for storing one or more preservation fluids. Additionally, the cap 12 and tube 14 can be configured to securely mate with one another in order to provide a secure containment of at least the sample bodily fluids for storing and shipping. Furthermore, the mechanism by which may be implemented in the sample collection device 10 for securely mating the cap 12 and the tube 14 may prevent disengagement between the cap 12 and the tube 14. One benefit of preventing disengagement between the cap 12 and the tube 14 is that it can prevent at least, for example, contamination of the sample contained in the tube and

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exposure of any preservation solutions (which may be toxic) to the sample donor, such as those contained in the cap 12.

FIG. 1A shows an example interior chamber 16 of the cap 12 which may be defined by at least one outer wall 24 and at least one inner wall 18 according to some embodiments. The at least one inner wall 18 may further define an interior space 20 and an aperture 22. In addition, the outer wall 24 may include one or more cap engagement features 34 along at least one side of the outer wall 24 for engaging the tube 14. For example, and shown in FIG. 1A, an inside surface 26 of the outer wall 24 can include one or more cap engagement features 34, such as threads, for engaging and mating with one or more complimentary tube engagement features 38, such as threads, associated with the tube 14. The tube 14 may be comprised of at least one containment wall 32 which may define a reservoir 40 for collecting and storing sample body fluids, such as saliva or urine. An outer surface 30 of the containment wall 32 may include the one or more tube engagement features 28, such as threads.

The cap 12 may further include an aperture 22 having one or more aperture engagement features 42, such as threads. In addition, the cap 12 may include a blocking member 46 which may have one or more blocking member engagement features 44, such as threads, for engaging the aperture engagement features 42. For example, the blocking member 46 may be removably coupled to the aperture 22 such that when the blocking member is secured to the aperture, one or more fluids or materials, may be contained within the interior space 20 of the cap. However, upon decoupling of the blocking member 46 to the aperture 22, the one or more fluids or materials may be released from the interior space 20 in the cap 12. For example, once the cap 12 has at least been partially secured to the tube 14, the blocking member 46 may be decoupled from the aperture 22, thereafter allowing fluids or materials in the interior space 20 to be released into the reservoir 40 of the tube 14. The one or more fluids or materials contained in the interior space 20 in the cap 12 may assist in preserving the sample body fluids contained in the reservoir 40 of the tube 14 during at least storage and shipping. Any of the engagement features discussed herein may be any number of engagement features for allowing temporary or permanent engagement between two parts or features of the sample collection device 10 and are not limited to the examples discussed in this disclosure.

The blocking member 46 may also include one or more coupling features 48 which may allow one or more coupling members 50 comprising a part of the tube 14 to engage and couple with the coupling features 48. The coupling between the coupling features 48 and coupling members 50 can assist in decoupling the blocking member 46 from the aperture 22. For example, as the cap 12 is secured to the tube 14, the coupling member 50 may engage and interact with the coupling feature 48 of the blocking member 46, such as similar to the head of a screw driver interacting with the head of a screw. The blocking member 46 may be threadably engaged with threaded aperture engagement features, and the coupling and interaction of the coupling feature 48 and coupling member 50 may cause the threaded engagement between the blocking member 46 and the aperture 22 to be released. The threaded engagement between the blocking member 46 and the aperture 22 may be released, for example, due to rotation of the blocking member 46 relative to the aperture 22. Any number of releasable engagements may be used to engage the blocking member 46 with the aperture 22 such that the engagement between the blocking member 46 and the aperture 22 may be released upon securing the cap to the tube 14. Similarly, any number of

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features may be integrated in the sample collection device **10** which may allow containment of a solution in a part of the cap **12** or tube **14** such that the solution is not released until the cap is at least partially secured to the tube **14**.

The tube **14** in FIG. 1A is shown by way of example as having a coupling member **50** in the shape of a square peg which is complementary to a square shaped indent comprising the coupling feature **48** in the blocking member **46**. Furthermore, the coupling member **50** can be centrally located within the tube **14** and the coupling feature may be centrally located on the bottom of the blocking member **46**. Therefore, upon threaded engagement between the cap **12** and the tube **14**, the square peg coupling member **50** may extend into and engage the square shaped indent coupling feature **48** in the blocking member **46**, thus preventing the blocking member **46** from rotating relative to the coupling member **50**. However, although the blocking member **46** may be prevented from rotating relative to the coupling member **50**, the blocking member **46** may rotate relative to the aperture **22** and become disengaged from the aperture **22**, such as from releasing the threaded engagement between the blocking member **46** and aperture **22**. FIG. 1B shows an example coupling member **50** secured to an inner surface **52** of the containment wall of the tube **14** by more than one cross-member **54**. The one or more cross members **54** can assist in securing the position of the coupling member **50** while allowing space for the passage of fluids or materials into the reservoir **40**.

An example method of use of a sample collection device **10** can include the sample collection device **10** supplied with sample preservation fluid in the interior space **20** of the cap **12**, and with the blocking member **46** threadably engaged with the aperture **22** in order to contain the sample preservation fluid in the interior space **20**. Sample fluid, such as saliva or urine, may then be placed in the reservoir **40** of the tube **14** by a donor. The cap **12** can then be screwed onto the tube **14**. Screwing the cap **12** onto the tube **14** may cause the coupling member **50** in the tube **14** to engage the coupling feature **48** of the blocking member **46** and unscrew the blocking member **48** from the aperture **22** and into the interior space **20** of the cap **12**. Decoupling the blocking member **48** from the aperture **22** can allow the sample preservation fluid to flow into the reservoir **40** of the tube **40**. After release of the sample preservation fluid into the reservoir **40** of the tube **14**, the sample preservation fluid can mix with the donor's sample fluid, thereby preserving the donor's sample fluid.

While shown as a square peg in this illustration, the coupling member **50** of the tube **14** can be any shape that is complementary in shape with the coupling feature **48** of the blocking member **46** such that it allows the blocking member **46** to decouple from the aperture **22**. The coupling feature **48** can be either in the blocking member **46** or the tube **14**, and the complimentary coupling member **50** may be either in the tube **14** or blocking member **46**, respectively. Other shapes will be evident to one skilled in the art, including, without limitation, a slot and a tab, like a regular screwdriver and screw, or a cross-shaped pair, like a Phillips screwdriver and screw.

An additional embodiment of the sample collection device **100** is shown by way of example in FIGS. 2A and 2B. The sample collection device **100** may include one or more coupling members **50** and complimentary coupling feature **48** which may be placed eccentrically from either the cap **12** or tube **14**. As shown in FIG. 2B, less material and parts may be required for this embodiment to work properly, such as the coupling member **50** maintaining proper positioning by

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only one cross-member **54**. Although the coupling member **50** is shown as being held in position by only one cross-member **54** extending from the containment wall **32** of the tube **14**, any number of configurations and cross-members **54** may be used to position the coupling member **50** without departing from the scope of this disclosure.

Another embodiment of the sample collection device **200** is shown by way of example in FIGS. 3A-3C. More specifically, FIG. 3A shows a cross section of the cap **12** prior to being coupled to the tube **14**. The cap **12** can include an outer wall **24** and cap engaging members **34** along an inside surface **26** of the outer wall **24**. The interior space **20** may be at least partially defined by at least one of an inner wall **18** or outer wall **24** of the cap **12**. Furthermore, the inner wall **18** can include engagement features **60**, such as threads, along a surface of the inner wall **18**. The inner wall **18** may further define an aperture **22** which may be open or closed depending on the position of an annular blocking member **62** relative to the aperture **22**. When the aperture **22** is closed such that the annular blocking member **62** is covering the aperture **22**, fluid or material, such as sample preservation fluid or material **70**, that may be contained in the interior space **20** may not be allowed to travel outside of the interior space **20**, as shown in FIG. 3A. However, when the aperture **22** is open such that the annular blocking member **62** is not covering the aperture **22**, the fluid or material **70** that may be contained in the interior space **20** may be allowed to travel outside of the interior space **20**, such as into the reservoir **40** of the tube **14**, as shown in FIG. 3B. The fluid or material **70** contained in the interior space may be beneficial for preserving sample **72**, such as body fluids (i.e., saliva, urine, etc.) placed in the reservoir **40** of the tube **14**, similarly as described above. Furthermore, any number of mechanisms may prevent the sample preserving fluid or material **72** from being released from the interior space **20** until the cap **12** is at least partially secured to the tube **14**.

In the embodiment shown by way of example in FIGS. 3A-3C, the annular blocking member **62** may be configured to interact with one or more features, such as a coupling member **50**, of the tube **14** such that as the cap **12** is being securely coupled to the tube **14**, the one or more features of either the tube **14** or annular blocking member **62** can cause the annular blocking member **62** to move from a position where the annular blocking member **62** is covering the aperture **22** to a position where the annular blocking member **62** is not covering the aperture **22**, thus allowing the sample preserving fluid or material **72** to release from the interior space **20** and interact with the sample **72**.

FIG. 3C shows a cross section of the tube **14**, having a containment wall **32** defining a reservoir **40** for sample collection. The tube **14** can include a coupling member **50** for engaging the coupling feature **48** of the annular blocking member **62**.

An example method of use of a sample collection device **200** can include the sample collection device **200** supplied with sample preservation fluid **70** in the interior space **20** of the cap **12**, and with the annular blocking member **62** covering the aperture **22** in order to prevent the passage of sample preservation fluid **70** through the aperture **22**. In this embodiment, sample fluid **72**, such as saliva or urine, can be placed in the reservoir **40** of the tube **14**. The cap **12** may then be securely coupled, such as threadably engaged, onto the tube **14** causing the coupling features **48** of the annular blocking member **62** to engage the coupling member **50** of the tube **14**. The annular blocking member **62** can then threadably engage the engagement features, such as threads, along the side of the inner walls. This can cause the annular

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blocking member 62 to move away from the aperture 22 so that it no longer covers the aperture 22. This, in turn, can release at least some of the sample preservation fluid 70 into the reservoir 40 of the tube 14, where it can mix with the sample fluid 72, thereby preserving it.

In some embodiments, the sample collection device 300, as shown by way of example in FIGS. 4A and 4B, cap 12 includes at least one coupling feature or a wedge 90 which is shaped and configured to interact with a complimenting coupling feature or a flange 92 of the tube 14. In this embodiment, the wedge 90 and flange 92 are extending along an inside surface of the cap 12 and tube 14. For example, when the cap 12 is coupled to the tube 14, the wedge 90 can engage the flange 92 and form a secure engagement between the cap 12 and the tube 14. Furthermore, once the wedge 90 and flange 92 have been completely engaged with each other, such as the locked configuration 96 shown by way of example in FIG. 4B, the engagement between the wedge 90 and the flange 92 may not be releasable by at least the sample donor. Therefore, once the cap 12 becomes engaged to the tube 14 such that the wedge 90 and flange 92 are securely engaged with each other, the cap 12 may no longer be disengaged from the tube 14 by at least the sample donor. This can prevent at least the sample donor from contaminating the sample body fluid that was deposited in the tube 14, as well as protect the sample donor from contact with the sample preservation solution. FIG. 4B shows sample embodiments of the unlocked configuration 94 and locked configuration 96 between the wedge 90 and flange 92.

In some embodiments, the sample collection device 400, as shown by way of example in FIGS. 5A and 5B, the wedge 90 and flange 92 are extending along an outside surface of the cap 12 and tube 14, respectively. FIG. 5B shows sample embodiments of the unlocked configuration 94 and locked configuration 96 between the wedge 90 and flange 92.

In some embodiments, the sample collection device 500, as shown by way of example in FIG. 6, where the cap 12 includes one or more sealed cavities 110 containing a sealing substance 112, such as glue. Any one sealed cavity 110 may be either operatively associated or positioned adjacent engagement features 34, such as threads, on the cap 12 such that when the cap 12 is coupled to the tube 14 the one or more sealed cavities 110 may be broken by one or more features or end 150 of the tube 12. Once the sealed cavity 110 is broken, a sealing substance 112, such as glue, may be released from the sealed cavity 110 and cause the cap 12 to become permanently secured to the tube 14.

Any number of features may be included with the cap 12 or tube 14 which may assist in preventing unwanted decoupling of the cap 12 from the tube 14, such as to prevent contamination. Additionally or alternatively, either the cap 12 or tube 14 may include a "tamper evident" feature 160 which may become altered such that it can be known to a user or sample collector if the cap 12 has been unfavorably decoupled from the tube 14. As shown by way of example in FIGS. 7A and 7B, the cap 12 may include a tamper evident feature 160 which may be comprised of a ring that is releasably attached to the open end 162 of the cap 12 such that when the cap 12 is unfavorably decoupled from the tube 14, the tamper evident feature 160 can permanently release its attachment from the cap 12, as shown in FIG. 7B. Once the tamper evident feature 160 is permanently detached from the cap 12, any observer of the cap 12 can determine that the cap 12 had been unfavorably decoupled from the tube 12, thus providing a warning of sample contamination, for example.

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Those skilled in the art will recognize that numerous equivalent embodiments can be used to obtain the benefits provided by the sample collection devices disclosed herein. For example, while this specification refers to certain elements being in the cap 12, and others in the tube 14, one skilled in the art would recognize that reversing the elements in the cap 12 to be in the tube 14 and vice-versa, would be an equivalent.

In some embodiments, a solution for preserving cells in one or more bodily fluids, such as saliva and urine, is disclosed. The solution for preserving cells may be beneficial for further separation into cell types and downstream molecular analysis that allows for storage of cells in the body fluid to retain their antigenicity and cellular architecture. The solution may contain at least one chemical fixing agent, such as but not limited to paraformaldehyde, and at least one protease inhibitor. In some embodiments, the solution may further contain one or more of at least one antimicrobial agent, and serum proteins from human and/or other animal species. The solution can be buffered at a pH from between about 6.4 to about 8.4, preferably from between about 7.2 to about 7.6.

For purposes of the disclosure, "preserving cells" means preventing the cells from having their antigens degraded, such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome. The "epigenome" means the state or pattern of alteration of genomic DNA by covalent modification of the DNA or of proteins bound to the DNA. Examples of such alteration include methylation at the 5 position of cytosine in a CpG dinucleotide, acetylation of lysine residues of histones, and other heritable or non-heritable changes that do not result from changes in the underlying DNA sequence.

In some embodiments, concentrations of agents in the following description can be those of the sample preserving solution itself. Depending upon the bodily fluid, and in the case of saliva, about an equal volume of solution and body fluid can be mixed together. This preferably results in the cells from the body fluids retaining their antigenicity and DNA integrity for at least one week at room temperature.

In some embodiments of the disclosure, the volume of preservation solution held within the device and deployed may be between about 100 and about 500 ml, which is relevant, for example, for the preservation of cells in urine. As such, the preservation solution for urine may be anywhere between about ten times (10x) concentrated solution to a one-point five time (1.5x) solution for urine.

A "chemical fixing agent", according to some embodiments, is a chemical cross-linking compound used to alter cell components such that the cells resist degradation. The chemical fixing agents can also serve to cross-link histones and other DNA-binding proteins to the DNA. Such agents may be known in the art and include, without limitation, paraformaldehyde, formaldehyde, formalin, aldehydes, alcohol, oxidizing agents, Mercurials, Picrates, Hepes-glutamic acid buffer-mediated organic solvent protection effect (HOPE), fixative combinations such as Zambonis fixative, combinations of aldehydes, and synthetic cross-linking reagents. In some embodiments, the chemical fixing agent is paraformaldehyde. In some embodiments, the chemical fixing agent is present at a concentration of about 1% (v/v).

To protect the cells from degradation by proteases present in the body fluids, in some embodiments, the solution can contain at least one protease inhibitor. In some embodiments, the protease inhibitor can be selected from the group consisting of Aspartic protease inhibitors, Cysteine protease inhibitors, Metalloprotease inhibitors, Serine protease

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inhibitors (e.g., serpins), Threonine protease inhibitors, Trypsin inhibitors, and Kunitz STI protease inhibitor. Some specific, non-limiting, examples include sodium azide, PMSF, Aprotinin, leupeptin, pepstatin, natural or synthetic proteinase inhibitors, and cocktail mixtures of protease inhibitors. Suitable concentrations of these inhibitors can include, without limitation, PMSF (Phenylmethylsulfonyl fluoride) Serine proteases at about 0.1-1 mM, Benzamidine Serine proteases at about 1 mM, Pepstatin A Acid proteases at about 1 µg/ml, Leupeptin Thiol proteases at about 1 µg/ml, Aprotinin Serine proteases at about 5 µg/ml, and Antipain Thiol proteases at about 1 µg/ml. In certain embodiments, the protease inhibitor is sodium azide at a concentration of about 0.01% (w/v).

To prevent damage to the cells from microbial contamination, some embodiments of the solution contain at least one antimicrobial agent. Suitable antimicrobial agents include, without limitation, antibacterial and antifungal antibiotics.

Preservation of cell architecture is enhanced by the presence of serum proteins, which may optionally be added to the solution in some embodiments. Additionally serum proteins may be used to neutralize osmotic difference between cells and solution. These can be from human or other animal sources. In some cases, whole serum may be used. For example, fetal bovine serum may be added, in some embodiments at about 1% (v/v).

The solution according to the disclosure may include any combination of the foregoing embodiments.

In some embodiments of the disclosure, a method for preserving cells in one or more bodily fluids is disclosed. The method for preserving the cells can comprise contacting the body fluids with the solution according to the present disclosure. The body fluids can contain a variety of cell types and the cells in the body fluids can be preserved by the solution according to the present disclosure. While not critical to the present disclosure, a ratio of solution to body fluids of from about 1 to 1 is typically used.

The following examples are intended to further illustrate some embodiments of the solutions and methods for preserving cells in body fluids and are not to be construed to limit the scope of this disclosure.

For example, a solution of PBS pH 7.4, 1% Paraformaldehyde, 1% FBS, and 0.01% NaN₃ can be added at a 1:1 ration with saliva, then T-cells can be purified and DNA extracted. The results of such a process are shown in FIG. 8. These results can demonstrate that the integrity of the antigenicity and DNA of T-cells was maintained for at least one week.

In some embodiments of the present disclosure, a method is disclosed which provides a sample of one or more body fluids, such as saliva or urine, comprising chemically fixed cells, and optionally centrifuging the body fluid sample to separate DNA and other soluble material from a pellet of cells including bacteria and debris. The method can further include enriching white blood cells, including lymphocyte cells, from other contents of the pellet. Additionally, specific cells may be isolated using antibodies conjugated to magnetic beads targeted to cell specific markers.

In some embodiments, the disclosure provides a method for isolating a particular type of white blood cell, specifically including, but not limited to lymphocytes, from bodily fluids (i.e., saliva, urine, etc.), comprising, for example one or more (and in some embodiments, several or all of the steps): providing a body fluid sample comprising chemically fixed cells, optionally centrifuging the body fluid sample to obtain a pellet comprising cells, optionally resuspending the pellet

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in buffer, subjecting the re-suspended pellet to density gradient separation to obtain a layer of a mixture of white blood cell types (including lymphocytes), contacting the mixture of cell types with a solution containing specific binding agents for an epitope found on a particular type of white blood cell, and separating the particular type of white blood cell (including lymphocytes) from the mixture of white blood cell types.

In some embodiments, the specific binding agents can include magnetic beads coupled to antibodies specific to an epitope found on a particular type of white blood cell, and separating may comprise magnetically separating the particular type of white blood cell (including lymphocytes) from the mixture of white blood cell types, though any method (and corresponding system/device) for separating cell types from one another is within the scope of this disclosure. Magnetic separation is but one method for doing so.

The cells can be chemically fixed prior to being subjected to the method according to this disclosure. The cells can be chemically fixed by, e.g., contacting a sample of saliva with a chemical fixation solution. This is done to preserve the cells over time at ambient temperatures. This can also allow for a complete study of the epigenome as it allows histone modifications and other protein-DNA interactions to be studied from the deposited body fluid samples. Histones must be chemically fixed to the DNA in order to be studied. Without fixation, the histones generally cannot remain bound to the DNA and the proteins can degrade over time.

In some embodiments, the buffer can comprise sodium azide, the buffer can comprise phosphate buffered saline and sodium azide. In some embodiments, the buffer may further comprise fetal bovine serum. In some embodiments, the buffer is at a pH from between about 7.2 to about 7.6.

In some embodiments, the cells are washed once in buffer. This in practice removes soluble material and in the case of saliva it removes what has been classified as the "buccal" layer (Dos-Santos et al., 2009).

In some embodiments, the mixture of white blood cells is washed one or more times in buffer prior to separating. This is preferably done to remove any remaining density gradient solution from the mixture of cell types.

In the process, the antibodies may bind to the particular type of white blood cells, thus binding the particular type of white blood cells to the magnetic beads. The particular type of white blood cells can then be separated from any other cell types by placing the magnetic beads in a magnetic field and removing any remaining liquid to obtain isolated cells of the particular type of white blood cells.

In some embodiments, the particular type of white blood cells can be a lymphocyte, where the lymphocyte may be a T-cell. In such embodiments, the antibodies used may be specific to an antigen specific to T-cells (e.g., the antigen being CD4). In some embodiments, the isolated blood cells may then be frozen prior to further processing, such as prior to epigenetic analysis.

The following example is intended to further illustrate an example method embodiment of the present disclosure and is not intended to limit the scope of the disclosure.

Example: Isolating T-Cells from a Bodily Fluid
(e.g., Saliva)

Saliva is collected, and the saliva is mixed with preservation solution. The cells are then pelleted by centrifugation and the processing solution is removed. The cells are then re-suspended in about 6 ml buffer (PBS, pH 7.4), 1% FBS,

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0.01% NaN₃), then washed once in a buffer and repelleted. The pellet are resuspended in about 6 mL PBS-15 FBS-.01% NaN₃ and subjected to density gradient centrifugation using 1.082-1.072 g/ml of Ficoll® (GE Healthcare). The white-blood cells are spun to the interface of the polysaccharides and buffer while the bacteria, debris, and any other particulate matter were pelleted at the bottom of the tube. The cells are extracted from the tube and placed in a new tube. The cells are then washed in Hank's Balanced Salt Solution once and then washed with the PBS-NaN₃-FBS buffer once to remove remaining density gradient solution that may have been taken while extracting the white blood cells from the interface.

The sample now includes highly enriched white-blood cells with minimal bacteria and minimal debris. This step can also greatly decrease other cell types, such as epithelial cells. The cells can then be incubated in buffer (PBS-NaN₃-FBS) with antibody targeted against CD4 conjugated to magnetic beads (Dynabeads® Invitrogen®). The samples can then be placed in a magnetic field, the beads brought to the side of the tube, and the liquid removed. The liquid may contain everything not bound to the beads through the antibody. The T-cells can be bound to the antibody and not removed due to the magnetic field. The beads and the attached cells can be washed in buffer to eliminate any non-specific or weak binding of other cells, bacteria, or other debris found in bodily fluids, such as saliva or urine. The cells can then be frozen for later downstream processing and analysis. The isolation of T-cells can be confirmed by light microscopy (T-cells are very distinct compared to epithelial cells and bacteria) (see FIG. 9). Additionally, flow cytometry and F.A.C.S. analysis using antibodies against CD3, CD4, and CD8 can confirm visual assessment of the isolated cells. The T-cells may then be titrated from the body fluid to determine the number of T-cells per unit of body fluid (ml) in order to determine the amount of body fluid, such as saliva or urine, for an adequate number of cells for downstream experimentation (see FIGS. 9 and 10). The isolated cells can be shown to have DNA devoid of degradation and appropriate for downstream use (see FIG. 8).

Any and all references to publications or other documents, including but not limited to, patents, patent applications, articles, webpages, books, etc., presented in the present application, are herein incorporated by reference in their entirety.

Although a few variations have been described in detail above, other modifications are possible. For example, any logic flow depicted in the accompanying figures and described herein does not require the particular order shown, or sequential order, to achieve desirable results. Other implementations may be within the scope of at least some of the following exemplary claims.

Example embodiments of the devices, systems and methods have been described herein. As noted elsewhere, these embodiments have been described for illustrative purposes only and are not limiting. Other embodiments are possible and are covered by the disclosure, which will be apparent from the teachings contained herein. Thus, the breadth and scope of the disclosure should not be limited by any of the above-described embodiments but should be defined only in accordance with claims supported by the present disclosure and their equivalents. Moreover, embodiments of the subject disclosure may include methods, systems and devices which may further include any and all elements from any other disclosed methods, systems, and devices, including any and all elements corresponding to collection, preservation, separating and isolating of cells from bodily fluids (e.g., saliva,

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urine), as well as the collection of other substances, including toxic and/or hazardous substances/fluids (as well as the preservation, separating and isolation of components thereof). In other words, elements from one or another disclosed embodiments may be interchangeable with elements from other disclosed embodiments.

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What is claimed is:

1. A kit for collecting and preserving a biological sample, the kit comprising:

- a sample collection vessel, the sample collection vessel comprising:
 - a sample collection reservoir having an opening configured to receive the biological sample from a user into the sample collection reservoir;
 - a connection member disposed on an exterior portion of the sample collection vessel and adjacent to the opening;
- a cap, the cap comprising:
 - a reagent chamber configured to store a reagent; and
 - a complementary connection member configured to engage the connection member of the sample collection vessel; and
- a movable annular valve configured to associate with the cap and with the opening of the sample collection reservoir, the movable annular valve comprising:
 - an inner cylinder in fluid-tight association with the cap and comprising a sidewall, the sidewall comprising a fluid vent; and
 - an outer cylinder in fluid-tight association with the inner cylinder and associated with the opening of the sample collection reservoir, the outer cylinder comprising an aperture defined by an interior sidewall of the outer cylinder, wherein the aperture accommodates at least a portion of the inner cylinder, wherein the interior sidewall obstructs the fluid vent when the movable annular valve is closed, and wherein the interior sidewall does not obstruct the fluid vent when the movable annular valve is open.

2. The kit of claim 1, wherein the outer cylinder comprises threads on the interior sidewall configured to mate with threads on an exterior sidewall of the inner cylinder, and wherein a distal portion of the inner cylinder moves through the aperture when the respective threads are unscrewed.

3. The kit of claim 1, wherein the outer cylinder comprises a sample collection reservoir sealing surface configured to create a fluid-tight seal between the outer cylinder and the opening of the sample collection reservoir when the outer cylinder is associated with the sample collection reservoir.

4. The kit of claim 1, further comprising a funnel configured to associate with the sample collection vessel and to guide receipt of a biological sample from a user into the sample collection reservoir of the sample collection vessel.

5. The kit of claim 1, wherein the connection member comprises one of a pushed connection, a rotated connection, a screwed connection, and a snap-fit connection.

6. The kit of claim 1, wherein the connection member and the complementary connection member each comprise threads.

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7. The kit of claim 6, wherein the threads of the complementary connection member comprise a plurality of internal threads of the cap.

8. The kit of claim 1, wherein the kit comprises a separable two-piece kit, the sample collection vessel comprising a first piece of the separable two-piece kit, and the movable annular valve associated with the cap comprising a second piece of the separable two-piece kit.

9. The kit of claim 1, wherein the outer cylinder comprises threads on the interior sidewall configured to mate with threads on an exterior sidewall of the inner cylinder.

10. The kit of claim 1, wherein the inner cylinder additionally comprises a reagent retention chamber, and wherein the reagent retention chamber is in fluid communication with the reagent chamber of the cap when the inner cylinder is associated with the cap.

11. The kit of claim 3, wherein a diameter of an outer wall of the inner cylinder is substantially equal to a diameter of the inner wall of the outer cylinder such that when the outer cylinder is associated with the inner cylinder, the fluid-tight connection is created therebetween.

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12. The kit of claim 1, wherein association of the cap with the sample collection vessel is configured to cause a distal portion of the inner cylinder to move through the aperture defined by the interior sidewall of the outer cylinder to expose the fluid vent defined by the distal portion of the inner cylinder.

13. The kit of claim 12, wherein the outer cylinder comprises threads on the interior sidewall configured to mate with threads on an exterior sidewall of the inner cylinder, and the respective threads are uncoupled when the distal portion of the inner cylinder moves through the aperture.

14. The kit of claim 12, wherein the outer cylinder comprises a sample collection reservoir sealing surface configured to create a fluid-tight seal between the outer cylinder and the opening of the sample collection reservoir when the outer cylinder is associated with the sample collection reservoir.

15. The kit of claim 1, wherein the movable annular valve is configured to close when the cap is at least partially disassociated from the sample collection vessel.

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Circuit Rule 32(b) because it contains 11,902 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f) and Federal Circuit Rule 32(b)(2), as determined by the word-counting feature of Microsoft Word.

This brief complies with the typeface requirement of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in a proportionally spaced typeface, including serifs, using Microsoft Word in Times New Roman 14-point font.

Dated: September 28, 2023

/s/ Brian R. Matsui